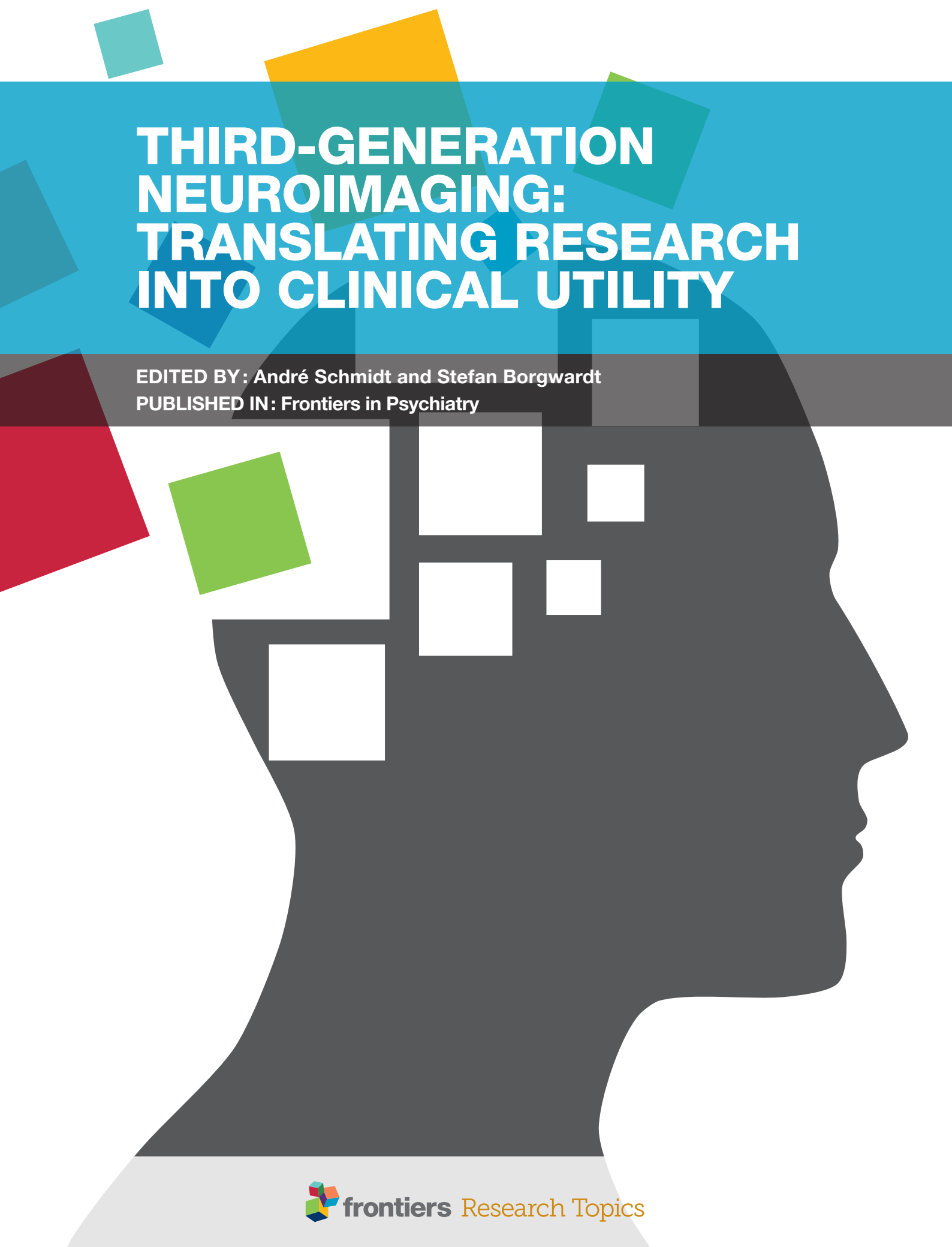
THIRD-GENERATION NEUROIMAGING: TRANSLATING RESEARCH INTO CLINICAL UTILITY

EDITED BY: André Schmidt and Stefan Borgwardt
PUBLISHED IN: Frontiers in Psychiatry



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frontiers

ISSN 1664-8714
ISBN 978-2-88945-044-2
DOI 10.3389/978-2-88945-044-2

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THIRD-GENERATION NEUROIMAGING: TRANSLATING RESEARCH INTO CLINICAL UTILITY

Topic Editors:
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Psychiatric imaging needs to move away from simple investigations of the neurobiology underling the early phases of psychiatric diseases to translate imaging findings in the clinical field targeting clinical outcomes including transition, remission and response to preventative interventions. This research topic aims to bring psychiatric neuroimaging studies towards translational impacts in clinical practice, suggesting that brain abnormalities may be of potential use for detecting clinical outcomes as treatment response. First-generation psychiatric neuroimaging focused on simple structural brain alterations associated with the neurobiology of the illness. These early studies adopted imaging methods mainly including computerized tomography (CT) to investigate brain size. Second-generation psychiatric neuroimaging studies benefited from more sophisticated techniques which included structural methods (sMRI) coupled with whole-brain automated methods (voxel based morphometry, VBM), white-matter methods (diffusion tensor imaging, DTI and tractography), functional methods (functional magnetic resonance imaging, fMRI) and advanced neurochemical imaging (PET techniques addressing receptor bindings and pre/post synaptic functions, magnetic resonance spectroscopy, MRS) and sophisticated meta-analytical imaging methods. However, no consistent or reliable anatomical or functional brain alterations have been univocally associated with any psychiatric disorder and no clinical applications have been developed in psychiatric neuroimaging.

There is thus urgent need of psychiatric imaging to move towards third-generation paradigms. In this research topic, these novel neuroimaging studies here requested to move away from simple investigations of the neurobiology to translate imaging findings in the clinical field targeting longitudinal outcomes including transition, remission and response to preventative interventions. With respect to methods, the most recent neuroimaging approaches (e.g. structural and functional MRI, EEG, DTI, spectroscopy, PET) are welcome. Third generation psychiatric imaging studies including multimodal approaches, multi-center analyses, mega-analyses, effective connectivity, dynamic causal modelling, support vector machines, structural equation modelling, or graph theory analysis are highly appreciated. Furthermore, these third-generation imaging studies may benefit from the incorporation of new sources of neurobiological information such as whole genome sequencing, proteomic, lipidomic and

expression profiles and cellular models derived from recent induced pluripotent stem cells research. We collect Original Research, Reviews, Mini-Reviews, Book Review, Clinical Case Study, Clinical Trial, Editorial, General Commentary, Hypothesis & Theory, Methods, Mini Opinion, Perspective, and Technology Report from international researcher and clinicians in this field. The purpose of this research topic is intended to provide the field with current third-generation neuroimaging approaches in translational psychiatry that is hoped to improve and create therapeutic options for psychiatric diseases.

Citation: Schmidt, A., Borgwardt, S., eds. (2016). Third-Generation Neuroimaging: Translating Research into Clinical Utility. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-044-2

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frontiers in Psychiatry

EDITORIAL
published: 12 October 2016
doi: 10.3389/fpsyt.2016.00170

Editorial: Third-Generation Neuroimaging: Translating Research into Clinical Utility

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Keywords: psychiatry, neuroimaging, prediction, transition, remission, treatment responses

The Editorial on the Research Topic

Third-Generation Neuroimaging: Translating Research into Clinical Utility

As yet, no reliable structural or functional brain marker has been univocally associated with any psychiatric disorder, and no clinical applications have been developed in psychiatric neuroimaging (1–4). There is thus urgent need of psychiatric imaging to move toward third-generation paradigms. First-generation psychiatric neuroimaging focused on simple structural brain alterations associated with the neurobiology of the illness. These early studies adopted imaging methods mainly including computerized tomography (CT) to investigate brain size (5). Second-generation psychiatric neuroimaging studies benefited from more sophisticated techniques, which included structural techniques such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), functional approaches such as task-related or resting-state functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) and neurochemical measurements like positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single-photon emission computed tomography (SPECT). However, by using these powerful non-invasive measurements, psychiatric imaging needs to move away from simple investigations of the neurobiology underling the early phases of psychiatric diseases in order to translate imaging findings into daily clinical routines, targeting clinical outcomes including transition, remission, and response to preventative treatment scenarios (1, 2, 6–11).

The aim of this research topic is to provide the field with an overview of current third-generation neuroimaging approaches in translational psychiatry that is hoped to improve and create therapeutic options for psychiatric diseases. This Research Topic includes articles indicating the potential of specific network connectivity analyses for inferring on the pathophysiological mechanisms of schizophrenia (Silverstein et al.), autism spectrum disorder (Crippa et al.), or suicidal behavior (Serafini et al.), or how they may help to predict the cognitive enhancing effect of pharmacological agents across disorders (van Amelsvoort and Hernaus) or psychotherapeutic interventions in patients with ADHD (Bachmann et al.) and schizophrenia and comorbid substance misuse problems (Wojtalik et al.). However, one article also emphasizes the importance of further second-generation imaging to investigate specific symptoms in a systematic manner before third-generation imaging can be informed (de Cates and Broome). Further contributions are suggesting advanced optical topography (Ho et al.), ^{18}F-FDG PET (Kowoll et al.), or EEG microstates (Rieger et al.) or beta oscillation analyses (Ghorashi and Spencer) as promising approaches to guide third-generation imaging across disorders (Ho et al.) or in schizophrenia [Ghorashi and Spencer; Rieger et al.], while others argue for the fusion of multimodal imaging modalities (Bellani et al.; Chiapponi et al.; O'Halloran et al.). Multimodal approaches, which integrate brain activation and connectivity patterns with metabolic measurements, are also proposed to gain a better

OPEN ACCESS

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *22 August 2016*
Accepted: *26 September 2016*
Published: *12 October 2016*

Citation:
Schmidt A and Borgwardt S (2016) Editorial: Third-Generation Neuroimaging: Translating Research into Clinical Utility. Front. Psychiatry 7:170. doi: 10.3389/fpsyt.2016.00170

understanding of the neuropathology underlying basic symptom in psychosis (Schultze-Lutter et al.). The current Research Topic also reveals the clinical utility of machine learning methods using multimodal imaging data in identifying individuals at high risk for psychosis (Valli et al.) and predicting outcomes across psychiatric populations (O'Halloran et al.; Schnack and Kahn), as well as of real-time fMRI (Dyck et al.; Fovet et al.; Gerin et al.) in treating symptoms of PTSD (Gerin et al.) and auditory–verbal hallucinations in schizophrenia (Dyck et al.; Fovet et al.). Finally, this topic outlines a theoretical framework how Hierarchical Bayesian Models of functional neuroimaging data may help to establish diagnostic test in autism spectrum disorder (Haker et al.).

This issue is intended to provide a useful framework for further third-generation imaging investigations aiming at predicting clinical outcomes, such as transition, remission, and treatment responses in early phases of different psychiatric diseases. These types of analyses might help to improve and develop novel therapeutic scenarios. We would like to thank all the authors and reviewers for their valuable contributions, as well as the Editorial Office for their help in the editing process.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 03 August 2016
doi: 10.3389/fpsyt.2016.00132

Inferring the Dysconnection Syndrome in Schizophrenia: Interpretational Considerations on Methods for the Network Analyses of fMRI Data

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Schizophrenia has long been considered one of the most intractable psychiatric conditions. Its etiology is likely polygenic, and its symptoms are hypothesized to result from complex aberrations in network-level neuronal activity. While easily identifiable by psychiatrists based on clear behavioral signs, the biological substrate of the disease remains poorly understood. Here, we discuss current trends and key concepts in the theoretical framework surrounding schizophrenia and critically discuss network approaches applied to neuroimaging data that can illuminate the correlates of the illness. We first consider a theoretical framework encompassing basic principles of brain function ranging from neural units toward perspectives of network function. Next, we outline the strengths and limitations of several fMRI-based analytic methodologies for assessing *in vivo* brain network function, including undirected and directed functional connectivity and effective connectivity. The underlying assumptions of each approach for modeling fMRI data are treated in some quantitative detail, allowing for assessment of the utility of each for generating inferences about brain networks relevant to schizophrenia. fMRI and the analyses of fMRI signals provide a limited, yet vibrant platform from which to test specific hypotheses about brain network dysfunction in schizophrenia. Carefully considered and applied connectivity measures have the power to illuminate loss or change of function at the network level, thus providing insight into the underlying neurobiology which gives rise to the emergent symptoms seen in the altered cognition and behavior of schizophrenia patients.

Keywords: brain networks, fMRI methods, schizophrenia, connectivity analysis, dysconnection syndrome

OPEN ACCESS

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *16 June 2016*
Accepted: *15 July 2016*
Published: *03 August 2016*

Citation:
Silverstein BH, Bressler SL and Diwadkar VA (2016) Inferring the Dysconnection Syndrome in Schizophrenia: Interpretational Considerations on Methods for the Network Analyses of fMRI Data. Front. Psychiatry 7:132. doi: 10.3389/fpsyt.2016.00132

INTRODUCTION

Schizophrenia is the consummate "epigenetic puzzle" (1). Psychiatrists, for the most part, know it when they see it in the clinic (2), yet its biological *origins* are utterly obscure, given that its etiology and genetic bases are poorly understood. We seem to *know* much but *understand* very little (3). Scientists have settled on the view that schizophrenia is a polygenic disorder (4, 5) where multiple genes (that themselves exert pleotropic effects) confer vulnerability, but wherein

the frank symptoms of the disorder themselves emerge from a complex (and plausibly in-deterministic) genetic-development-environmental interplay (6–9).

Lack of understanding of causative pathways (in addition to other factors such as phenotypic heterogeneity) is a limiting constraint on efforts at prevention, early intervention, and/or treatment of schizophrenia (10). Yet, as is evident in other fields of medicine (most notably cardiology and oncology), successful medical treatment and management does not necessarily depend on identifying deterministic causal pathways toward disease. Rather, understanding of vulnerability measures is sufficient, as long as there is a clear characterization of the pathophysiologic *mechanisms* underlying the disease. A grasp of basic biological mechanisms drives the development of targeted therapies while simultaneously providing objective biomarkers that can inform treatment efficacy (11, 12). Psychiatry has long been criticized for focusing on emergent *effects* of disease, while having an insufficient focus on understanding *mechanisms* of disease. As a result, many emergent effects are insufficiently constrained by analytic approaches designed to explicitly characterize mechanisms. The argument is that these limitations essentially limit nosology and treatment (13). Here, we reiterate the widely held view that the mechanisms of diseases like schizophrenia will most profitably be understood by focusing on, to put it simply, how the brain is "not working." More pertinently, we accept the position that the current state of acquiring and modeling brain signals suggests that brain–behavior relationships may best be understood from the position of *macroscopic* brain network interactions (14), a scale that may most proximately map cognitive and sensorimotor function to its underlying correlates. We are aligned with the position that these investigations are a matter of discovery, and subscribe to the distinction between "true" models of brain function (whatever those may be) and "likely" models of brain function (15), where the former are theoretical constructs, whereas the latter are empirically discoverable from neuroimaging data. We will assert that these ontological subtleties are of direct (and not merely academic) relevance to the study of schizophrenia: if understanding brain mechanisms subserving normal function is a process of discovery, by corollary, understanding these in the context of schizophrenia is also a process of discovery. Moreover, this process is constrained by quantitative models, and the assumptions therein, that are applied to any class of neuroimaging data. Thus, understanding disconnection in schizophrenia is an *inference*, and the class of models applied will provide constraints on the type of inference that can be drawn (16).

What follows is a compendium of previously advanced ideas motivating schizophrenia as a syndrome of functional disconnection, or more accurately, "dysconnection": this is generally understood as the abnormal integration of signals across the brain (17). These ideas are not novel to this review and, in fact, have remained in place since the earliest conceptions of schizophrenia itself. However, over time the idea of dysconnection, once a general construct, has been systematically hewn to a point where it can be seen as having clear bases in translational neuroscience (18–20). We willfully restrict our scope to the approaches used in the analyses of functional magnetic resonance imaging (fMRI) signals. Thus, while much of what we review strictly extrapolates to fMRI studies in schizophrenia, many of the quantitative approaches that we review are not specific to fMRI time series analyses.

Much has been written about fMRI, its neurophysiological bases, the relative advantages of the signal, and its limitations for assessing brain function (21–24). Moreover, the comparative merits and demerits of different imaging techniques for discovering connection and disconnection in the brain is a viable topic but beyond our scope (25, 26). As a technique, fMRI is neither mercurial nor worthless; rather the technique provides access to credible signals that under appropriate analytic constraints can tell us something interesting about how the brain works.

ORGAN SYSTEMS AND PHENOTYPES

As understood from the early origins of psychiatric taxonomy, the body's only organ system of direct relevance to schizophrenia (and indeed all psychiatric illnesses) is the brain, and the brain's *functional* properties were seen as the most salient in this regard (27, 28). Psychiatric phenotypes have always fundamentally been defined by behavioral abnormalities (29). If the "mind–body" problem is narrowly defined as the problem of understanding how mental states emerge from the physical states of the body (30, 31), then understanding pathophysiological mechanisms underlying schizophrenia is a special case of the mind–body problem. That is, if "neural" processes drive normal behavior, then abnormal behavior (i.e., such as those observed in schizophrenia) must result from abnormal neural processes. A challenge then is to identify abnormal neural mechanisms that lie in a straightforward relationship with the phenotypic characteristics of schizophrenia itself. Given that the dialectic regarding the mind–body problem remains active, it is self-evident that understanding neural mechanisms associated with schizophrenia is a non-trivial problem.

The term "dysconnection" itself can be construed as having at least two somewhat distinct meanings. In one, the term represents the sense in which Blueler and Kraepelin thought of schizophrenia: a kind of "splitting of the mind" (32, 33). In all likelihood, this meaning carried only a vague relationship to neurobiological considerations. In his writing, Bleuler clearly related the idea to loss of cohesion in intellectual faculties, but the work of these great neurologists predated modern neuroscience, and thus they were not privy to the multitude of experimental methods and theoretical ideas available now. Indeed, in their time, understanding of brain function was largely grounded in phrenological/localizationist theories wherein the outputs of individual brain regions, emergent as their "functions," were assumed to map onto anatomical structures in relatively direct ways (34, 35).

A second, more literal sense of dysconnection (or "disconnection" as originally proposed), is quite explicitly neurobiological: in this view, schizophrenia is an emergent behavioral phenotype resulting from profound alternations in the connectivity of the brain's anatomic and functional pathways (18, 36, 37). Just as structural connectivity loosely constrains the brain's functional architecture (38, 39), impaired anatomical connectivity most likely offers loose constraints on the inability of the brain in schizophrenia to integrate functional signals across regions in

both non-task and task-active states (40, 41). It has been asserted that normal perception and cognition rely on a cortico-cortical phase synchronization mechanism that operates in conjunction with reentry to provide context for local cortical computations by way of inter–areal interactions (42). This mechanism normally provides a balance of integration and segregation to complex dynamic cortical networks, and schizophrenia is likely to be marked by a shift toward segregation such that local cortical areas express their information content without benefit of the context normally provided by interaction with other areas (43, 44). A modern view of the dysconnection syndrome constitutes a program for neurobiological discovery and offers the promise for arriving at fundamental insights on brain mechanisms that mediate the emergence of the illness.

FROM LOCALIZATION TO NETWORK FUNCTION: NEUROLOGY AND NEUROPSYCHIATRY

The localizational model was in part driven by the technologies available for collecting data from the brain. In essence, the model relied on systematic analyses of functional loss in patients with localizable neurological lesions (45). Lesion-based models were characterized by rudimentary system's-based approaches toward brain–behavior relationships, the Wernicke-Geschwind model of speech comprehension and production (46) serving as a good example. However, their accuracy was compromised by impoverished data and, more fundamentally, by the untenable (yet implicit) assumption that brain regions existed in fairly specific one-to-one relationships with overt behavior (34). Among others, Wernicke and Luria should be given credit for creating a hybrid model that distinguishes between elementary functions expressed by individual brain regions and complex functions that are properties of distributed systems of brain areas (42). Thus, as we understand it now, early neurology turned out to be an impoverished framework for understanding both the complexities of normal brain function and the complexities of disorders like schizophrenia.

The "neuron theory," largely motivated by the work of Santiago Ramón y Cajal (47), emerged in the late nineteenth century. The theory experimentally developed the idea of neurons as functional units, the extracellular outputs of which reflect basic properties of behaviors (both simple and relatively complex). The neuron theory has been a (perhaps *the*) *sina qua non* of modern neuroscience. The explosion of single unit extracellular recordings has provided a wealth of insight into the complex response properties of single units and the extent of (particularly sensorimotor) function that these responses explain (48, 49). Nonetheless, theories of structure–function relationships based on single unit recordings are ultimately subject to the same ontological limitations as phrenology (50). Cognition and behavior (normal or pathological) are far too complex to reduce to single brain regions, let alone units. Indeed, as connectivity is a basic property of neurons (which connect through axons and synapses), connectivity studies are a natural direction for neuroscience. If anything, neurological models, neuron theories, and lesion studies provide evidence of only one of the multiple organizing principles of brain function at the macroscopic scale: the principle of relative specialization of function. This principle suggests that brain regions are more likely to sub serve one class of functions than another (51, 52). Relative specialization is a question of degree. There is little about the brain that is strictly "categorical." Rather, it is more likely that the degree of specialization is relatively strong in sensorimotor or modality specific regions ("unimodal" regions), but relatively weak in regions involved in sensorimotor integration and "higher" behaviors [or "heteromodal" regions (53, 54)]. Clearly then, a different and parallel principle of functional brain organization is needed that more directly speaks to the emergence of complexity, and by corollary, the emergence of complex disorders of the brain.

If we treat the single neuron theory as the first revolution in modern neuroscience, the application of complex systems theories, and the operationalization of these analytic frameworks for understanding the brain must constitute the second (55). Ludwig von Bertalanffy's work on general systems theory continues to reverberate in modern neuroscience (56) as the drive to explain processes in terms of interactions between the components of a system gains force (57). This is particularly pressing in terms of understanding how cognitive ontologies arise from the brain (39, 58). The functional integration of signals across brain regions presents itself as a parallel organizing principle of brain function (52, 59), and if complex cognitive ontologies arise from brain network interactions, and schizophrenia itself is in part defined as a "cognitive" illness (10), then it is reasonable to assert that the disorder results from impaired functional integration of signals across brain regions, i.e., brain network dysfunction.

The history of neuroscience is characterized by a synergistic relationship between methods and theory (60, 61). Theoretical advances in the neurobiology of schizophrenia have been crucially driven by developments in *in vivo* whole brain functional neuroimaging, in particular fMRI. fMRI is based on complex hemodynamic spatiotemporal signals (62, 63) that themselves lie at the apex of a series of complex neuronal (and presumably neurochemical) processes; these processes exist in uncertain relationships with the overt fMRI signal (22, 61). Thus uncovering brain network function and dysfunction from fMRI time series data has been termed a process of "reverse engineering" and "network discovery"; what must be engineered or discovered are the hidden states of brain function that give rise to fMRI signals (55, 64). If understanding brain network interactions is a process of quantitative discovery, then understanding of what the inferred processes are must be grounded in quantitative models applied to fMRI time series data (65).

MODELS FOR INFERRING NETWORK FUNCTION: WHAT CAN BE INFERRED?

Distinct classes of analytical techniques have been fruitfully applied to fMRI time series data (38, 66, 67), and much of what follows is a synthesis of published and influential reviews. Our goal is to selectively sample and distil for the reader quantitative bases of analytic methods, and reveal what they render as knowable about brain connectivity and, by extension, dysconnectivity.

Ultimately, connectivity is an inference that is based in the quantitative models used to assess it. This inference inherits the advantages and limitations of the models applied to discover these patterns in overt fMRI signals. In understanding brain network dysfunction in schizophrenia (or any psychiatric condition) exposure to the fundamentals of the analytic methods is a necessity for understanding what is being modeled (and ultimately inferred).

Functional connectivity (FC) and effective connectivity (EC) are two broad classes of analytic methods for assessing connectivity. FC generally refers to the statistical relationship (in the time domain) of two spatially distinct signals. In fMRI data, these analyses typically constitute calculations of bivariate temporal correlations usually at zero-lag thus ignoring potentially useful information about timing relations between BOLD time series drawn from distinct regions of interest, wherein strongly correlated or anti-correlated regions are "functionally connected" (68). In general, co-variations in time series signals are heavily used in assessing functional relations between elements of complex systems (69) and provide a useful though limited framework for network discovery. In the context of fMRI data, these methods have been noted for some limitations. First, they are sensitive to the variability of hemodynamic response functions (HRFs) across brain regions. Second, due to the limited temporal information in the signal, they generally must rely on "zero-lag" analyses, thus ignoring potentially useful information about timing relationships between BOLD time series. Moreover, they lack functional transitivity, in that the techniques are insensitive to divining functional relationships between regions that are correlated with a mediating time series (55, 70, 71). Coherence is a complementary measure of FC that estimates linear time–invariant relationships between multiple time series even at phase delays. As a spectral analog of bivariate correlational analyses, coherence accounts for phase relations in the cross-correlational function (while limited by the bandwidth of the hemodynamic response) (72). Finally, we also note the value of Wiener–Granger Causality (73), a method for inferring functional relationships between regions based on temporal predictability between time series. Granger Causality has also been referred to as directed FC (dFC), distinguishing it from undirected FC (uFC) methods that depend on correlative statistics (74, 75).

The standard notion of EC is that it captures the effect that one neuronal population exerts over another (regardless of the scale at which these interactions are assessed) (52). More specifically, true EC depends on capturing the relatively precise timing relationships between *neuronal* populations (76), thus depending on the applied models to capture the temporal dynamics of neuronal populations. Implicit within the definition of EC is that these techniques explicitly seek to model "causative" relations between brain regions and that they depend on generative network architectures of the brain. A causal relationship is both an ontologically different claim than simple statistical covariation, but importantly therefore also includes information about the direction of influences between regions (77). Moreover, EC entails a notion of estimated "coupling": that is, the determination that a causal influence exists between neuronal populations fundamentally relies on constructing a *generative model* of that coupling. This means that understanding EC is a question of model comparison: what model of the brain is most likely to have generated the observed data, where each model itself constitutes a hypothesis of brain function in that context (78). The implicit and explicit assumptions of each approach and the models implemented therein exert constraints in inferences regarding brain network connectivity, and by extension, about dysconnectivity in schizophrenia. Beyond this, modeling can help unravel the physiological mechanisms underlying causal influences in the brain. That is, what is the effect exerted by the neurons in one brain area on those in another area. It is plausible that inter-regional interactions are modulatory, shaping the activity generated by the internal dynamics of the local area (42). To evaluate this hypothesis, we need to be informed by (a) the location on the recipient neurons of the synapses coming from transmitting neurons in other areas and (b) the neurophysiological effect of inter-regional influence (e.g., how does it change the sub threshold membrane potential?). Moreover, model *structure* plays an important inferential role. The likely generative model for schizophrenia may be different than that for controls, and the differences in model structure may provide valuable information regarding the architecture of the disease (41). These issues are revisited later.

UNDIRECTED FUNCTIONAL CONNECTIVITY TECHNIQUES BASED ON BIVARIATE CORRELATIONAL APPROACHES

Bivariate correlational approaches toward fMRI time series data are by far the most commonly applied measure of assessing temporal relationships between regions of interest. These methods make weak assumptions regarding functional transactions between regions, are frequently used in an exploratory manner, and do not provide measures of coupling in the manner of other techniques (see more on this aspect below) (75). Generally considered, this class of FC analysis mines statistical dependencies in the time domain (for fMRI data) between disparate time series. This approach is represented in:

$$\rho_{x,y} = \frac{\mathrm{cov}(x,y)}{\sigma_x \sigma_y}$$

In this generic form, the correlation coefficient, $\rho_{x,y}$, of two independent time series x and y, is equal to the covariance of x and y normalized by the product of the SDs, σ, of both signals. FC is an *emergent* statistical property of inter-relationships between time series, such as provided by the fMRI BOLD signal. Crucially, FC analyses have not usually relied on biophysical models linking neuronal with hemodynamic responses (79), which means the notion of "coupling" in uFC analyses does not extend beyond the statistical realm. Thus, as with any emergent statistical result, the only "model" of function tested by uFC methods is the null model, that is, testing against an absence of significant correlation between brain regions. As a result, these methods make few assumptions about temporal context, the temporal scale, or resolution of any putative underlying process.

The weak assumptions relating to processes, however, also confer some advantages for this class of FC measures. There is greater statistical reliability with shorter time series than measures that make stronger assumptions or that require more precisely modeled time series (as will be seen with Granger Causality techniques). Moreover, weak assumptions also mean that uFC analyses are relatively robust to contributions of filtering or slice-time correction applied to fMRI data that can artificially disrupt the fine-scale temporal structure of the signal, thus producing spurious causality (we discuss the relationship between temporal information and causal inference in detail below).

uFC TECHNIQUES BASED ON COHERENCE

Coherence is a complementary approach to time-domain uFC that has enjoyed widespread use with EEG data, but has been generally under-utilized for fMRI analysis, largely because limited temporal information in the fMRI signal preempts complex spectral analyses of fMRI signals. Coherence is a frequency-domain measure of how well one signal linearly predicts a second in a time–invariant fashion. The most common approach defines coherence as the magnitude of the cross-spectrum of two signals, *x* and *y*, normalized to the power spectra of each signal. Specifically, magnitude squared coherence, Coh_{xy}, at a given frequency, *f*, can be defined as

$$Coh_{xy}(f) = \frac{\left|P_{xy}(f)\right|^2}{P_{xx}(f)P_{yy}(f)}$$

where P_{xy} is the cross-spectrum, and P_{xx} and P_{yy} are the power spectra of both signals. As with correlation, the metric is scaled ($0 \le Coh_{xy}(f) \le 1$), such that 0 represents no linear relationship between the two signals, and 1 represents the ability to perfectly predict one signal from the other. In order to reduce the variance and edge artifacts that can be introduced by windowing data in the time domain prior to a Fourier transform, coherence is often calculated using Welch's modified periodogram averaging method (80). An estimation of the interregional coherence can then be calculated for each resulting frequency bin or averaged over the frequency range inhabited by the hemodynamic response function (HRF), typically defined as 0–0.15 Hz (70).

The time–invariant property of coherence allows the measure to assess relationships between time series beyond the zero-lag constraint. As previously noted, variations in the shape of the HRF along with time delays may offset the temporal progression of two related BOLD responses in functionally related brain regions. This property of fMRI signals presents a challenge for the sensitivity of correlation analyses, because correlations will decrease toward 0 as a function of increasing lag between two otherwise synchronized signals. For example, if two brain regions are co-modulated by a task, but with a time delay or with different hemodynamic responses, they may be synchronized with a phase lag. This can be generalized as the relationship between a sine function, $\sin(t)$, and a second identical, but phase-shifted sine function, $\sin(t+\theta)$. As the phase shift, θ, progresses from 0 to $\frac{\pi}{2}$, the zero-lag correlation decreases to 0, then further to −1 as θ approaches π. However, a linear relationship still exists between the two signals, and coherence between the two sine waves will remain at 1. In other words, coherence allows for phase shifts or temporal lags when scoring the FC. Thus, while both zero-lag correlation and coherence are able to capture the relationship between the signals when the phase lag is near 0 or π, lags around $\frac{\pi}{2}$ are lost to zero-lag correlation [for more details on this method, see Ref. (71, 80)].

Spurious non-zero values of coherence can arise in the analysis of physiological time-series data simply due to the spectral properties of the signals (81). An effective method for correcting this bias is the use of surrogate data sets (81–83). Here, the time series data are shuffled, thus disrupting the phase relationships but preserving the statistical distribution of the spectral content. After multiple iterations, the mean and SD of the surrogate results can be compared to the experimental results. Any values of coherence exceeding the 95th percentile of the surrogate data distribution can be considered significant.

Correlative analyses are undirected by definition – hence the label "undirected FC" above. An interpretational limitation is that these methods are agnostic regarding directional influences between network nodes. Undirected connectivity/coherence analyses have a different footprint in the analyses of electrophysiological signals where within- and inter-regional coherence can be assessed at multiple frequencies (84, 85), each of which reflect somewhat distinct functional properties of cortical function. The temporal resolution of fMRI data does not afford this luxury. Nonetheless, there has been an exuberant profusion of undirected FC techniques applied to the resting state fMRI. Combined with graph-theoretic methods, these applications have provided insight on network disorganization in schizophrenia (40, 44). A valuable extension of this work would be in understanding how these altered network hierarchies in schizophrenia are expressed in disconnection in a task-active state. However, such extension would require integrating multiple areas of focus, including within-subjects acquisition of resting *and* task-based data, and the implementation of multiple techniques for estimating connectivity (outlined herein). Nevertheless, we suspect that the value of uFC analyses alone in inferring disconnection in schizophrenia is limited. The applied statistical model for uFC is relatively impoverished and identifies emergent statistical properties of fMRI signals [see Ref. (16) for a more comprehensive treatment of these questions]. These emergent statistical properties are removed from biophysical models linking accumulative neuronal with hemodynamic responses (86) and therefore may be distant from mechanisms of brain function.

Understanding directional relations between network constituents is important for multiple reasons. While various brain areas have reciprocal structural connections, it is highly unlikely that directional relations will simply reflect structural connections. Moreover, for a variety of reasons, structural connectivity only offers lose constraints on the functional integration of signals. In terms of functional organization, it is very likely that the direction of information flow in the brain is of critical importance for organizing cognitive functions and consciousness. This has been

demonstrated from numerous studies of connectivity in both EEG and fMRI (87, 88). Moreover, directional effects are also important in the context of brain network hierarchies (53, 54). Control regions of the brain, including the dorsal prefrontal cortex and the anterior cingulate cortex enjoy higher hierarchical status within the overall system (74, 89, 90), suggesting that their functional transactions are likely to be asymmetric (91). Capturing these asymmetries will prove highly valuable, particularly in schizophrenia, which has frequently been characterized as a disorder of cognitive control (92–94). These considerations motivate quantitative FC methods that explicitly attempt to capture directional interactions between network constituents in health and schizophrenia. We next consider two directed FC methods, Granger Causality (73) and psychophysiological interaction (PPI) (95, 96).

FC TECHNIQUES BASED ON DIRECTIONAL APPROACHES

Psychophysiological Interaction

Since its introduction in 1997, PPI has constituted a widely used approach to directed FC (95). PPIs are constructed by extracting a time series from a seed region of interest and multiplying its activity with a stimulus function or regressor encoding the psychological context (95). This computation generates a regressor term that is used to capture variance in the time series of target voxels, as explained by the seed region, within the context of the task. Technically, signals that are highly predictable will produce a significant PPI effect but PPIs are readily distinguished from correlative methods. This follows because they test for second order dependencies. In other words, they test for a linear dependency of activity in the target region on activity in the seed or source region that itself depends upon another (psychological) variable. It is this high order, or interaction, effect that breaks the symmetry and endows PPI analyses with a directed nature. Strictly speaking, one could argue that PPIs reflect a simple (GLM) model of EC. However, we associate a PPI analysis with the inference that there are statistically significant second order dependencies; namely the interaction. As such, we will treat PPI analyses as a form of directed FC (i.e., statistical dependence).

The GLM approach to assessing PPIs provides a potentially more nuanced framework for modeling the time series data as it allows the model to co-vary out confounds. This is accomplished *via* a point-wise multiplication of the seed time series with a stimulus function and the inclusion of various sources of noise in the model (96). This product time series is then the interaction between the BOLD time series and the psychological task – the eponymous PPI. The interaction time series, along with both the task model and HRF time series, can then be used as regressors in the GLM, which separates the variance in the target signal associated with the psychological task, the HRF, and the interaction between the two signals (the psychological regressor and the response in the seed region). The equation below captures the directional bases of PPIs:

$$y_i = ay_0 + b\left(y_0 \times u\right) + cu + X\beta$$

The above is readily distinguishable from the typical GLM applied in activation models by the presence of the asymmetric interaction term $\left(y_0 \times u\right)$, in which regressing $\left(y_0 \times u\right)$ on y_i is asymmetric with regressing $\left(y_i \times u\right)$ on y_0 (55).

As with all modeling of fMRI signals, PPIs constitute an *a priori* conceptual model of brain function. The implicit model is that *contextual interactions* between seeds and targets can be characterized within a statistical framework. In this context, the choice of seed and the psychological context are free parameters of the model, and these choices must be well motivated by prior knowledge regarding task characteristics and the putative network profiles of the seed in an integrative network (94, 95, 97, 98). The simplicity of the PPI framework is advantageous as it affords rapid exploration of network profiles in normal and clinical populations (and differences between them). Nevertheless, this simplicity is also a limitation because comprehensive network interactions are rarely subsumed by pairwise interregional interactions. Moreover, PPIs are not defined by biophysical models linking neuronal with hemodynamic responses, and therefore they do not provide measures of neuronal coupling, limiting their neurobiological interpretation (95, 96).

Granger Causality

In treating the brain as a complex system, computational neuroscience has successfully coopted analytic tools that were initiated for other disciplines, where many data properties are shared with fMRI data – particularly the idea that functional aspects of the system interactions are "hidden" in time series data. Notable examples from physics and electrical engineering include time-frequency analyses, graph theoretical approaches, and information theoretic measures. GC is a measure of directed FC, which has its roots in the analysis of economic data (99). Since its import into the field of neuroscience, GC has been used extensively in estimating directed connectivity relationships in multiple modalities of brain imaging including EEG, MEG, and fMRI (73). GC can, in brief, by described by:

$$X_t = \sum_{j=1}^{m} \alpha_{2j} X_{t-j} + \sum_{j=1}^{m} \beta_{2j} Y_{t-j} + \varepsilon_{2t}$$

$$X_t = \sum_{j=1}^{m} \alpha_{1j} X_{t-j} + \varepsilon_{1t}$$

$$GC_{Y \to X} = ln\left(\frac{\Sigma_1}{\Sigma_2}\right)$$

where, $\Sigma_1 = \mathrm{Var}(\varepsilon_{1t})$ and $\Sigma_2 = \mathrm{Var}(\varepsilon_{2t})$. In GC, the estimated dFC depends on the model order and the estimated time lag between modeled time points in the two signals. Accordingly, appropriate specification of the time lag between different observations and the order or number of past observations included in the auto-regression model above are crucial for properly testing for GC influences. Generally, the appropriate time lags and model orders are unknown (although they can be estimated using procedures based upon mutual information and Bayesian model comparison). This means the ability of GC to make inferences

about FC – based on relatively slow dynamics – is potentially challenging [see Ref. (100, 101)]. It should be noted that correlation also suffers from a dependence on time lag, and important correlations may be missed by over-reliance on the lag-zero value.

In general, GC evaluations may cover a range of time lags up to a maximum value in order to search the parameter space for the correct lag. This approach has been demonstrated for transfer entropy, an information theoretic extension of GC. Lee et al. (87) define the information flow between two nodes as the maximum normalized transfer entropy found by scanning the time delay parameter space. This method has been successfully applied to electroencephalograph data in humans (87), as well as electrocorticograph data in rodents (102), allowing researchers to track changes in cortical information flow across changes in states of consciousness. However, given the limited temporal resolution of fMRI, the model order rarely extends beyond one time step.

Because GC relies on the temporal progression of time series to estimate causality, it is crucial that the ordering of the time series data remain unmodified. The convolution process used in finite- and infinite-response filters alters each data point based on both the previous data points and those succeeding it. After filtering, then, the value at any given time has been influenced not only by its past but also by its future, thus undermining the basic assumption of causal inferences. Convolution with a HRF can also affect the structure of time series, notable because as referred to earlier, HRFs can differ across brain regions. Several lines of work somewhat mitigate against these concerns. There is evidence that GC is invariant to HRF convolution (103), and as noted earlier, assessing directional asymmetries (i.e., direction is used as a condition of interest in the GLM) of GC coefficients between regional pairs can better constrain the interpretation of causal effects (104).

Notwithstanding the directed nature of the applied models, as with PPI, GC is limited by a lack of adequate bases in physiological underpinnings. The dynamics of interacting neural populations is considerably removed from the signals recorded by fMRI and subsequently entered into a GC calculation, and there is no extant physiological model to bridge it. Nevertheless with appropriately constrained research questions and experimental designs, GC (as with PPIs) provides a quantitative characterization of directional pairwise interactions between constituents of brain networks. These insights can provide meaningful perspectives on the nature of dysconnection in schizophrenia.

EFFECTIVE CONNECTIVITY TECHNIQUES

The term "effective" connectivity is the source of much confusion, but can be more clearly understood from the perspective of interactions between constituents of a complex system. From a mechanistic perspective, EC has been defined as the influence that one neural system exerts over another (76). EC models thus attempt to embody dynamic and timing relationships between system constituents, typically using elements of control theory (52). Because there is no reasonable sense of a "true" and veridical model of brain function that can be wholly derived from observed data (15), EC relies on a method for evaluating *competing* model architectures for a set of network nodes, any of which is a plausible generator of the observed data, but have inherently differing likelihoods of having done so (78). This competitive (and ultimately Bayesian) framework is essential for the process of model discovery and is largely absent from previously considered techniques of directed and undirected FC (though some elements are present in the evaluation of directional asymmetries using GC). These motivations for divining neuronally plausible network-based mechanisms are by themselves insufficient unless a mapping from neuronal responses to the generated hemodynamic response is implemented (86). Dynamic Causal Modeling (DCM) incorporates a Bayesian framework for network discovery while using biophysical models relating neuronal to hemodynamic responses.

Dynamic Causal Modeling

Dynamic causal modeling was introduced as a seminal framework for discovering mechanistic brain network function from fMRI (and other) data (105) and has subsequently received significant methodological inspection of its biophysical and probabilistic bases, and its reliability (106, 107). In its original conception, DCM represented the brain as a bilinear system (a lower order approximation for non-linearity) in which the inputs are the experimental conditions and the outputs are the hemodynamic response measured using fMRI. Because DCM is explicitly interested in modeling dynamics and changes in these dynamics in response to inputs, elements of control theory are incorporated where changes in network states are modeled using the following state differential equation:

$$\frac{dx}{dt} = \left(A + \sum_{j=1}^{m} u_j B^{(j)} \right) x + Cu$$

To be clear, this equation describes the dynamics of "network states" rather than of any physiological metrics. In other words, this is not an explicit physiological model. The state equation represents three differentiable components with large distinct bio-psychological extensions: here, A represents the matrix of endogenous coupling between brain regions. Simply speaking, this can be construed of as the hypothesized functional connectome underlying the evaluated model. The connections within any model represent a hypothesis on the pattern of connectivity. How the model is "wired" depends on a combination of priors that include reliably known connective pathways and/or explicit hypotheses for discovering which pathways may or may not exist independent of task-induced experimental changes. The variable $B^{(j)}$ represents the modulatory response in the network connections due to changes in experimental conditions u_j. Finally, C represents the direct driving input on particular regions as induced by the experimental conditions.

Network discovery with DCM relies on the identification of generative network architectures with the highest evidence given the observed fMRI data, thus testing hypotheses on an *a priori* defined model space. Thus, the space comprises neurobiologically plausible competing models, each representing hypotheses on the connective-architecture of the investigated neural system (78, 108, 109). Therefore, rather than using traditional goodness-of-fit metrics to assess the viability of an individual model, DCM

relies on evaluating these multiple neurobiologically plausible competing network models, wherein across competing models, specific network connections may be permuted, and these permuted connections specifically serve as hypotheses. Thus, across models, connections can be constrained or informed by known properties of neuroanatomy (110) or may be permuted with some agnosticism regarding the specifics of the underlying anatomy itself. More importantly, the method provides a plausible approach toward understanding how brain networks "work," by incorporating principles of both relative specialization and functional integration. By corollary EC methods provide a compelling context for understanding cases (such as schizophrenia) in which the brain does "not work" (111).

CHALLENGES FOR INFERRING CONNECTION AND DYSCONNECTION

Understanding *causal* antecedents of disease have historically driven the promise of successful medical intervention or preemption. This concept of *deterministic* causality is a fundamental assumption in medicinal discovery and practice. Illnesses have causes that can be determined and addressed. These causes may cut across biological, environmental, and epidemiological levels (112), yet it is commonly assumed that the causative pathway is, in fact, deterministic. Moreover, many medical successes have benefit from the relative simplicity of the structure–function relationships within the organs of relevance. For example, advances in cardiac or pulmonary treatment benefit from the relatively straightforward relationships between the structures of the heart or the lung, and their expression in function. Unfortunately, the brain proffers no simplicity in this regard. Rather, its structure (to the extent that it is fully knowable) provides relatively light constraints on its emergent functional interactions, and even more indeterminacy with respect to how overt behavior arises. This "degeneracy" is a significant challenge to assessing the brain's structure–function relationships (35) and degenerate structure–function mappings (i.e., many to one mappings) can also be observed in the relationship between functional and effective connectivity. In other words, there are many connectivity architectures of EC that can produce the same FC. We will consider an example based upon a common source below. Technically, this means that inferring EC from FC can be an ill-posed problem that necessarily calls for prior constraints and (abductive) inference, as we have carefully intimated in the Introduction.

For instance, should connectivity between two regions be established *via* a statistical model, the conclusion that the two regions have a direct relationship can always be undermined by the hypothetical existence of a third, undetected member of the system, though this possibility can be somewhat mitigated by knowledge of the anatomical connectivity structure of the areas under consideration (thus, region C may only be a candidate driver if it is anatomically known to project to regions A and B). Thus, a bivariate correlation between regions A and B, may be driven by (1) a functional or causal relationship in which A causes B and/or B causes A, or (2) regions A and B are both modulated by a third region, C, such that A and B are synchronized without directly interacting. If there is a different time delay between C and A than between C and B, this can even appear as a phase–lag relationship between regions A and B thus presenting as a directed FC relationship. However, given that methods such as GC are based on predictability, they can be used to establish a driving role for area C (113). Thus, demonstrating a directed relation based on any measure of predictability is superior to phase-lag measures in terms of what can be inferred. Nevertheless, although multivariate GC can account for a third time series and its influence on the system, this can only be modeled when the third time series has been identified and is measurable. If the third node in the system is unknown, then contribution toward the inference of connection remains unknown. These limitations are a particular example of the general problem of causal inferences in brain networks, and as has been forcefully argued and extensively discussed (114, 115), deriving *deterministic causal inferences* regarding brain network interactions may be a fundamentally untenable exercise. Not only might the etiology of schizophrenia remain obscure, but even the inference of brain network mechanisms that might inform the proximate causes of the illness may suffer from fundamental challenges. The potential contribution of hidden or latent nodes is, in principle, not a problem for models of EC like DCM. This is because one can use Bayesian model comparison to evaluate the probability of a hidden common source – by comparing models with and without hidden nodes.

WHAT ASPECT OF DYSCONNECTION IN SCHIZOPHRENIA CAN BE UNDERSTOOD FROM THE ANALYSES OF fMRI SIGNALS?

Figure 1 summarizes the methods visited in this overview, arranged in a two-dimensional conceptual space. The space carves out quadrants within which the methods are defined by their directionality (directed vs. undirected network interactions) and the relative "strength" of the methods (functional or effective connectivity), where "strength" can reasonably be construed of as the degree to which the parameters of connectivity models can be linked to biophysical processes or computation in real neuronal networks.

This is a parsimonious representation, yet provides a panoramic (and somewhat self-evident) overview of the different aspects of network dysfunction that can be inferred from each class of analytic approaches applied to fMRI time series data. Though we emphasize that the axes do not approach metric properties, we use weak ordinality to arrange the methods within the space to allow some contemplation of their strengths and weaknesses. For example, directed analyses may provide more interpretational value than undirected analyses, and EC approaches may, in principle, be more desirable than FC approaches. A crucial dimension not represented is tractability of implementation – both in terms of designing analyses and computationally implementing them. We note that this tractability is unevenly distributed within this space, yet is an issue of concern in the search for inferring dysfunction in schizophrenia. We also note

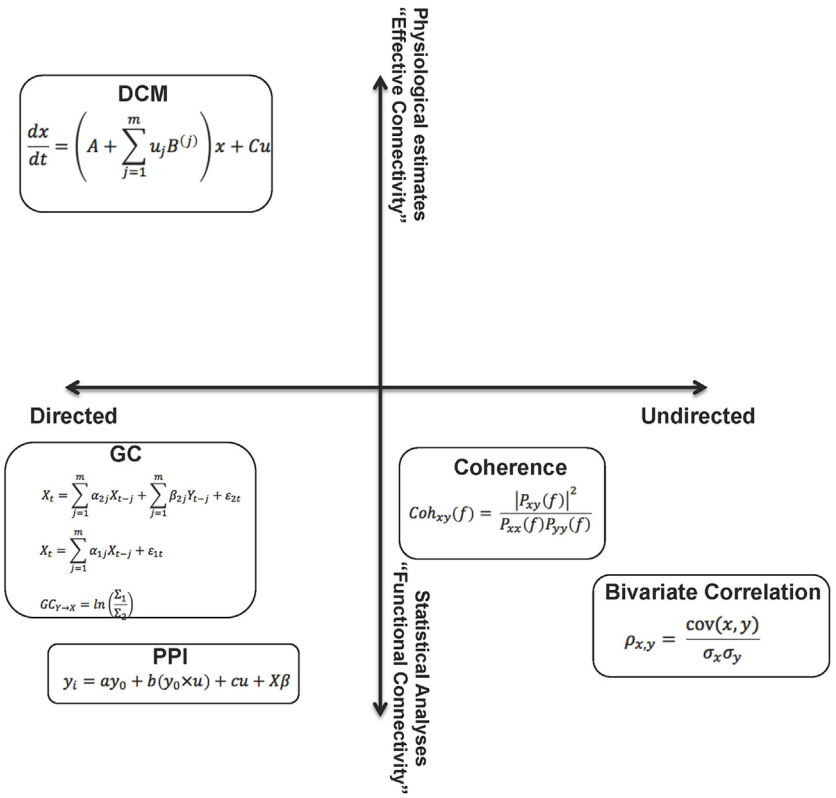

FIGURE 1 | The figure summarizes the methods visited in this overview, by placing them in a two dimensional "space." From this perspective, the relative (to each other) properties of these analytic methods are somewhat apparent on each dimension. These dimensions can be associated with the "strength" of each method. A reasonable characterization of "strength" can be the degree to which the parameters of the connectivity models can be linked to biophysical processes or computation in real neuronal networks. The constraints on parameters emerge from assumptions within the models (functional to effective connectivity) and also relate to the notion of directionality within models (directed to undirected). As noted in the text, though the space cannot be defined by metric properties, some aspects of ordinal relationships between the methods can be inferred.

that the motivation for this review relates to schizophrenia, yet the extensions are general across psychiatric illness (though the networks of focus within the brain may be idiosyncratic to the phenotypes of interest).

Is schizophrenia itself *tractable*? It is unclear whether all aspects of the etiology of this complex condition are knowable, yet inferring dysconnection in schizophrenia is a special case of inferring brain network function. In that sense, inferring the dysconnection syndrome is perhaps no more or no less tractable than understanding how macroscopic brain network interactions can be related to other overt or covert behaviors. We suggest that if fMRI has told us anything of significant value, it is that macroscopic brain network dynamics expressed at the scale of seconds can be successfully modeled to infer aspects of brain function. Theory and technique now offer avenues for inference and discovery that did not exist even in the recent past. The methods covered herein (and others) offer the prospect of inference and discovery that suggests the promise of significant mechanistic understanding of schizophrenia.

AUTHOR CONTRIBUTIONS

VD directed the writing of the manuscript and contributed the principle conceptual direction. SB provided important conceptual insight and technical language particularly relating to Granger Causality models. BS provided insights relating particularly to functional connectivity methods.

FUNDING

Preparation of this work was funded by support to VAD: a Career Development Chair from Wayne State University, the Thomas Gershenson Distinguished Faculty Fellowship from Wayne State University, the Lyckaki-Young Fund from the State of Michigan, the Prechter Family Bipolar Foundation, the Children's Hospital of Michigan Foundation, the Cohen Neuroscience Endowment, and the National Institute of Mental Health (MH 59299).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

MINI REVIEW
published: 23 February 2016
doi: 10.3389/fpsyt.2016.00020

Cortico-Cerebellar Connectivity in Autism Spectrum Disorder: What Do We Know So Far?

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Although the Autism Spectrum Disorder (ASD) is renowned to be a connectivity disorder and a condition characterized by cerebellar involvement, the connectivity between the cerebellum and other cortical brain regions is particularly underexamined. Indeed, converging evidence has recently suggested that the cerebellum could play a key role in the etiopathogenesis of ASD, since cerebellar anomalies have been consistently reported in ASD from the molecular to the behavioral level, and damage to the cerebellum early in development has been linked with signs of autistic features. In addition, current data have shown that the cerebellum is a key structure not only for sensory-motor control, but also for "higher functions," such as social cognition and emotion, through its extensive connections with cortical areas. The disruption of these circuits could be implicated in the wide range of autistic symptoms that the term "spectrum" connotes. In this review, we present and discuss the recent findings from imaging studies that investigated cortico-cerebellar connectivity in people with ASD. The literature is still too limited to allow for definitive conclusions; however, this brief review reveals substantial areas for future studies, underlining currently unmet research perspectives.

Keywords: cortico-cerebellar connectivity, autism spectrum disorders, autism, DTI, fMRI, resting-state fMRI

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Richard Eugene Frye, Children's Hospital Boston and Harvard University, USA
Megha Sharda, University of Montreal, Canada

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *01 December 2015*
Accepted: *09 February 2016*
Published: *23 February 2016*

Citation:
Crippa A, Del Vecchio G, Busti Ceccarelli S, Nobile M, Arrigoni F and Brambilla P (2016) Cortico-Cerebellar Connectivity in Autism Spectrum Disorder: What Do We Know So Far? Front. Psychiatry 7:20. doi: 10.3389/fpsyt.2016.00020

INTRODUCTION

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental disorder characterized by persistent social impairment, communication abnormalities, and restricted and repetitive behaviors (DSM-5) (1, 2). ASD is a complex condition with an average prevalence of about 1% worldwide (3), one in 68 U.S. children (4). Although high heritability estimates suggest a critical role for genetic factors (5), its etiology is generally considered multifactorial. It has been hypothesized that the heterogeneous phenotype of ASD could implicate a greater likelihood of abnormalities in the connectivity between different neural networks rather than alterations in a specific cerebral area (6). Over the last decade, the claim that ASD is a disorder of connectivity has been reliably supported by evidence from neuroimaging studies (7, 8), even though with mixed findings. On one hand, some studies have provided initial evidence of underconnectivity in ASD (9–11); on the other hand, another line of research has indicated overconnectivity in ASD,

arguing for an increased local and short-distance connectivity within the frontal cortex, with respect to reduced long-range connectivity between frontal lobes and posterior brain regions (12–14).

Two recent studies (15, 16) that analyzed the database of fMRI resting-state scans from the Autism Brain Imaging Data Exchange have revealed the occurrence of underconnectivity and overconnectivity in ASD, although with different topographical distributions. More precisely, overconnectivity seems to be primarily associated with subcortical regions, whereas hypoconnectivity appears to characterize the pattern of cortico-cortical and interhemispheric functional connectivity.

However, the connectivity between different brain areas with the cerebellum is still a particularly under-considered issue in ASD research. Although it was traditionally believed that the cerebellum was exclusively a motor structure (17), converging evidence suggested a role for the cerebellum in other "higher" functions, including language and cognition, as well as emotion (18–20). Indeed, neuroanatomical findings have clearly shown that the cerebellum can influence a number of neocortical areas, including premotor, prefrontal, and posterior parietal areas of the cerebral cortex, through polysynaptic circuits via thalamus and basal ganglia. These pathways subserved specifically different functions, such as movement, cognition, and social skills (21–24). On the basis of decades of anatomical and imaging data [see Ref. (25, 26, 27–30) for reviews], it has been suggested that the cerebellum could be primarily implicated in ASD (31, 32), with cognitive and behavioral effects beyond the difficulties in the motor domain (33, 34). In fact, a cerebellar dysfunction early in development has been associated with deficits in executive functions, visual-spatial processing, linguistic function, and affective regulation (35, 36), and even with social difficulties, such as avoidance of physical contact or gaze aversion, within a diagnosis of ASD (37). Moreover, Wang et al. (36) recently proposed that cerebellar damage in childhood may perturb the maturation of distant neocortical circuits during developmental sensitive periods through a "developmental diaschisis," increasing the risk for developing ASD.

Despite its connections with several brain areas and the well-known involvement of this structure in the disorder, few imaging studies have investigated the role of cerebro-cerebellar connections in ASD and correlations between cerebro-cerebellar connectivity and clinical measures. Considering this lack of evidence, we briefly summarized the recent imaging findings on cortico-cerebellar connectivity in ASD in order to (a) address strengths and pitfalls of previous studies and (b) explore potential strategies for future research. In addition, we aimed to understand whether disruptions of specific cortico-cerebellar circuits could be associated with specific difficulties in ASD or different phenotypes within the disorder. Publications for this review were identified from a PubMed search in November 2015 using terms related to autism, connectivity, magnetic resonance (MR) imaging, and cerebellum. This search was supplemented with other publications from the reference lists of all included citations, and from the personal reference databases of the authors.

DIFFUSION IMAGING STUDIES

Structural connectivity can be assessed *in vivo* using MR techniques like diffusion-weighted imaging (DWI) or Diffusion Tensor Imaging (DTI). These non-invasive techniques provide indirect quantitative measures of white matter integrity, such as fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity, by measuring water diffusion in the underlying tissue microstructure (38). Mean diffusivity is the average of the diffusion in the different directions of the space, and its values are related to the presence of barriers or obstacles, like cellular membranes and axons, which can interfere with the free water displacement within a voxel. When diffusion of water molecules is not the same along the three axes of the space (as in axons), it is called anisotropic, which means it has a preferential direction of displacement. Axial and radial diffusivity measure the entity of displacement along the principal and its perpendicular axis. FA values, which range between 0 and 1, are also a measure of anisotropy that seem to be related with myelination, axon diameter, and fiber coherence (39). High FA values denote well organized and normally myelinated axons that provide natural barriers to water movement within tissue. Lower FA values, in contrast, may reflect axonal loss and/or demyelination (39) as well as areas of crossing fibers. DWI allows for quantification of FA at voxel levels, whereas DTI, using different tracking algorithms, enables reconstruction of structural connections. An overview of the studies on structural connectivity between the cerebellum and different cerebral areas in ASD can be found in **Table 1** (40–45). When using the terms overconnectivity or underconnectivity in diffusion imaging studies, we refer here to connectivity disruption in terms of tissue organization.

The majority of results from diffusion imaging studies showed a weaker structural connectivity in participants with ASD, as indicated by decreased FA both in the superior cerebellar peduncles (40, 41, 44) and in intracerebellar circuitries (45). However, findings in the middle cerebellar peduncles did not yield consistent evidence. Shukla et al. (42) revealed reduced values of FA in adolescents with ASD; conversely, Sivaswamy et al. (43) found increased values of FA in the right middle cerebellar peduncle, although within a reverse asymmetry pattern in FA of the middle and inferior cerebellar peduncles. A quantitative tractography study (45), in which a newly developed method for DWI called the "independent component analysis with a ball and stick model" was used to reveal abnormally reduced volume and number of fibers between the cerebellar cortex and right ventral dentate nucleus, accompanied by decreased FA between the cerebellar cortex, right dorsal dentate nucleus, and bilateral ventral dentate nucleus. Alterations of FA in cerebellar structures are mainly, but not always, reported to occur in association with reduced axial diffusivity [Ref. (44, 45); but not Ref. (42)], in absence of abnormalities of mean or radial diffusion.

In respect to the relationship between white matter integrity, behavior, and ASD symptoms, Catani et al. (40) found a negative correlation between FA values in the right superior cerebellar peduncle and in the right short intracerebellar fibers, in addition to social difficulties as reported by a caregiver using ADI-R (46), a "gold standard" diagnostic interview tool for clinical diagnosis.

TABLE 1 | Diffusion imaging studies investigating cerebro-cerebellar connectivity in ASD.

Study	Participants (*N*, age range)	Methods	Findings	Relationship connectivity measures – behavior
Catani et al. (40)	15 Asperger, 16 HC, 18–49 years	DTI–ROI	↓ FA in the right superior cerebellar peduncle and in the right short intracerebellar fibers No differences in the mean diffusivity	Negative correlation between the ADI-R social domain score and FA of the left superior cerebellar peduncle
Brito et al. (41)	Eight with autism, eight HC, 6–12 years	DTI–ROI	↓ FA in the left superior cerebellar peduncle, and in the right and in the left middle cerebellar peduncles	NA
Shukla et al. (42)	26 ASD, 24 HC, 9–18 years	DTI–ROI	↓ FA in the middle cerebellar peduncle No differences in the mean diffusivity, axial or radial diffusion	No correlations with ADI or ADOS scores
Sivaswamy et al. (43)	27 ASD, 16 HC, 2.6–9 years	DTI–ROI	↑ Mean diffusivity of the bilateral superior cerebellar peduncles ↑ FA in the right middle cerebellar peduncle Reversed pattern of asymmetry in the FA of the middle and inferior cerebellar peduncles	NA
Hanaie et al. (44)	13 ASD, 11 HC, 5–14 years	DTI–ROI	↓ FA in the right superior cerebellar peduncle ↓ Axial diffusivity in the left superior cerebellar peduncle	Positive correlation between the M-ABC 2 total score and FA in the right superior cerebellar peduncle
Jeong et al. (45)	15 ASD, 14 HC, 3.6–13	DWI – ICA + BSM tractography	↓ Streamline volume and count between cerebellar cortex and the right VDN ↓ FA between cerebellar cortex and the right DDN, and VDN bilaterally ↓ Axial diffusivity between cerebellar cortex and the left DDN, and left VDN	Positive correlation between FA of right dorsal dentate nucleus and VABS 2 – daily living skills

ASD, autism spectrum disorder; HC, healthy controls; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; ICA + BSM, independent component analysis with a ball and stick model; ROI, region of interest; FA, fractional anisotropy; VDN, ventral dentate nucleus; DDN, dorsal dentate nucleus; NA, not assessed; ADI-R, Autism Diagnostic Interview-revised; M-ABC 2, Movement Assessment Battery for Children – second edition; VABS, Vineland Adaptive Behavioral Scales.

Moreover, Jeong et al. (45) depicted a relation between lower FA values between the cerebellar cortex and the right dorsal dentate nucleus, and between the ventral dentate nucleus bilaterally and poor daily living skills measured by Vineland Adaptive Behavioral Scales (47). Lastly, the motor abilities measured at Movement ABC-2 (48) were found to be positively correlated to FA in the right superior cerebellar peduncle (44). However, Shukla et al. (42) reported no relationship between DTI measures and clinical symptoms of ASD.

In sum, findings from diffusion imaging studies indicate underconnectivity – in reference to a different white matter integrity and coherence between participants – between the cerebellar main outflow pathways (i.e., the superior cerebellar peduncles) and the neocortex, and in intracerebellar circuitries that involve the dentate nucleus. Results for the middle and inferior cerebellar peduncles are not so consistent, with mixed reports of reduced and increased structural connectivity. Nevertheless, these findings altogether seem to suggest a possible abnormal connectivity between the cortical areas and the main afferent fibers of the cerebellum. Finally, the findings from the reviewed studies suggested some preliminary evidence of a relationship between the structural connectivity of the cerebellum and manifestations of ASD.

TASK-RELATED FUNCTIONAL IMAGING STUDIES

Functional brain connectivity can be effectively quantified during both task performance and rest by correlating variations of the blood-oxygen-level-dependent (BOLD) signal over time (49, 50). Different neuroanatomical regions are assumed to be functionally connected when the time courses of the BOLD fluctuations in these regions have synchronized patterns of activation (51). To the best of our knowledge, only three studies investigated the functional connectivity between cerebellum and cortical areas during task performance in ASD. Mostofsky et al. (52) assessed activation during a sequential finger tapping task in 13 children with high-functioning autism aged 8–12 years and in 13 age-matched typically developing peers, using functional magnetic resonance imaging (fMRI). The authors found activations in motor circuits across participants, which include contralateral pre/postcentral gyrus, ipsilateral anterior cerebellum (lobules IV/V), bilateral activation in the superior medial wall (BA6), and contralateral activation in the thalamus. However, children with typical development showed recruitment of cerebellar structure, i.e., the anterior lobe of the contralateral cerebellum (lobules IV/V) and ipsilateral anterior cerebellum, that is absent in autistic children. Conversely, the clinical group showed an increased activation of the supplementary motor area. In addition, a reduced functional connectivity within the motor circuits including premotor areas and the cerebellum was observed in autistic children, suggesting alterations in long-range connections in the fronto-cerebello-thalamo-frontal network.

Jack and Morris (53) directly investigated the relationship between functional connectivity and ASD features in an fMRI study on the neural bases of perception and use of human actions in imitation. Using psychophysiological interaction (PPI) analysis, the authors indicated an involvement of the network between posterior superior temporal sulcus (pSTS) – neocerebellum (i.e., Crus I) in social cognition in both adolescents with and without

TABLE 2 | Resting-state imaging studies investigating cerebro-cerebellar connectivity in ASD.

Study	Participants (*N*, age range)	Methods	Findings	Relationship connectivity measures – behavior
Padmanabhan et al. (56)	42 ASD, 48 HC, 8–36 years	ROI (striatal seed regions)	Different developmental trajectory of FC among striatum, cerebellar lobules VI and VIIa, and Crus I	No correlations with ADI-R score
Verly et al. (57)	19 ASD + LI, 23 HC, mean age (SD): 14.3 years (1.3), 14.0 years (1.5)	ROI (seed regions) plus voxel-based analysis	↓ FC within the cerebello-DLPF, cerebello-SMA, cerebello-IFG, and cerebello-premotor circuits	Negative correlation between the ASD severity factor and FC between the right cerebellum and left DLPF seed
Khan et al. (58)	28 ASD, 28 HC, 8–17 years	ROI	↑ Overall FC between cerebrum and cerebellum ↑ FC between cortical regions of one domain (motor or supramodal) and cerebellar regions of the other ↑ FC for the sensorimotor ROIs but ↓ FC for the supramodal ROIs	No correlations with ADI-R Negative correlation between the cerebellar FC with the right supramodal ROI and non-verbal IQ
Carper et al. (59)	44 ASD, 36 HC, 7–18 years	Seed regions	No group differences in FC between cerebellum and M1	No correlations between FC and clinical symptoms after correction for multiple comparisons
Dajani and Uddin (60)	53 ASD, 53 HC, three stratified groups: children <11 years, adolescents 11–18 years, adults ≥18 years [data from ABIDE (14)]	Regional Homogeneity (ReHo)	Children: ↓ ReHo in cerebellar lobule VI Adolescents: ↑ ReHo in cerebellar lobule IX Adults: ↓ ReHo in cerebellar vermis, bilateral lobule VI, and Crus I	Positive correlation between mean ReHo values and SCQ

ASD, autism spectrum disorder; LI, language impairment; HC, healthy controls; ROI, region of interest; FC, functional connectivity; DLPF, dorsolateral prefrontal; SMA, supplementary motor area; IFG, inferior frontal gyrus; ADI-R, Autism Diagnostic Interview-revised; SCQ, Social Communication Questionnaire.

ASD. Although PPI data did not differ between groups, the authors showed that functional coactivation of pSTS and Crus I could predict the social deficits in ASD, as rated by parents on a questionnaire assessing "mentalizing skills," (54) i.e., the ability to attribute mental states to others.

Recently, Kana et al. (55) examined the neural network underlying theory of mind, including the cerebellum, in high-functioning children and adolescents with autism while they were decoding the interactions between animated figures. The authors found a reduced cerebellar activation, particularly in Crus I, in participants with ASD in the theory of mind condition. Furthermore, they outlined reduced functional connectivity in ASD between the cerebellum and medial regions (i.e., medial prefrontal cortex and posterior cingulate cortex).

RESTING-STATE IMAGING STUDIES

Five recent studies that use resting state to assess cerebro-cerebellar connectivity were included in the present review (see **Table 2** for an overview).

Verly et al. (57) investigated the role of the cerebellum and its functional connectivity in the classic areas of the language network in children with ASD and language impairment. To do this, a verb generation fMRI task was first used to define language areas commonly active in participants with and without ASD. Afterward, the selected regions were used as seeds for resting-state analysis, in addition to the traditional voxel-based analysis. Results from both the seed-based and voxel-wise maps indicated a significantly reduced functional connectivity in ASD among cerebellum, Broca's, and Wernicke's areas. The authors interpreted this dissociation of cerebral and cerebellar language regions as a possible index of altered cerebellar modulation of language functioning.

The study by Khan et al. (58) is, to date, the first work that aimed to directly assess the cerebro-cerebellar connectivity in ASD. The authors used resting-state MRI to measure the functional connectivity between the cerebellum and seven bilateral cortical regions of interest (ROIs) in 28 children and adolescents with ASD compared to their typically developing peers. Cerebral regions were grouped in sensorimotor ROIs (premotor and primary motor cortices, somatosensory superior temporal cortex, and occipital lobe) and in supramodal ROIs (prefrontal cortex, posterior parietal cortex, and inferior and middle temporal gyri). Overall, the authors found a general cerebro-cerebellar overconnectivity in the ASD group. In addition, the analysis of the connections' domain-specificities revealed an increase in non-canonical links, i.e., in the connections between cortical regions of one domain (sensorimotor or supramodal) and cerebellar regions of the other. Furthermore, an increased cerebro-cerebellar connectivity was also found in sensorimotor circuitries at the expense of connectivity in supramodal "cognitive" networks (reduced in ASD).

Carper et al. (59) have recently investigated the anatomical and functional connectivity of the motor control system in children and adolescents with ASD compared to healthy controls. With regard to the connectivity between the cerebellum and M1, the authors did not find any group differences in functional connectivity.

Finally, the other two resting-state studies reviewed here aimed to assess the functional connectivity of the cerebellum across development (56, 60). Indeed, both studies were cross-sectional and recruited participants of different ages, from childhood to adulthood. Findings from these works consistently indicated

abnormal developmental trajectories of functional connectivity. Specifically, Padmanabhan et al. (56) found an increase of connectivity over development between cerebellar and subcortical regions (i.e., the striatum nucleus) in people with ASD, but a decrease in healthy controls. Dajani and Uddin (60) used regional homogeneity (ReHo) analysis to individuate local patterns of connectivity within the cerebellum. The authors were able to describe an age-specific pattern of short-range connectivity in ASD, with children and adults having lower ReHo in the cerebellum than controls, while adolescents exhibited an increased cerebellar local connectivity.

In respect to the relationship between functional connectivity and ASD features, findings from the study analyzed here are not entirely consistent. Indeed, no links between connectivity and "gold standard" clinical measures of ASD were observed (56, 58), although reduced connectivity seem to be accompanied by an increase in the severity of the disorder (57, 60), as assessed by the Social Communication Questionnaire [SCQ, Ref. (61)]. Lastly, lower values of connectivity between cerebellum and supramodal "cognitive" areas have been observed to be linked to higher non-verbal IQ (58).

SUMMARY AND FUTURE DIRECTIONS

In the present work, we aimed to provide an up-to-date overview of current findings on cortico-cerebellar connectivity in ASD. This issue represents an emerging field of interest for ASD research, following the hypothesis that ASD is a connectivity disorder associated with cerebellar dysfunctions. The cerebellum has been recently indicated as a key structure not only for sensory-motor control, but also for language, social cognition, and emotion, via its extensive connections with cortical areas (33–37). Although the literature is at a very early stage and more work on cortico-cerebellar connectivity is urgently needed, some preliminary suggestions can be drawn from the reviewed studies. Findings from task-related imaging studies showed a pattern of underconnectivity between the cerebellar outflow pathways and the neocortex, and in long-range fronto-cerebello-thalamo connections. Results from diffusion imaging studies are partly in line with these conclusions, although it is worth noting that this technique does not provide any direct measure of connectivity but is solely an index of fibers coherence and integrity. Significantly reduced long-range functional connectivity, among cerebral and cerebellar language regions, was also found in a resting-state study. However, results from afferent fibers of the cerebellum and from other resting-state studies indicated more complex, or even opposite, patterns of findings, disallowing any firm conclusion at this time. The causes of this discrepancy might be various, as the studies differed in many important methodological aspects. As clearly shown by Nair et al. (62), factors such as the type of analysis, the choice of seed placement, and the type of dataset can have a dramatic impact on results of functional connectivity studies in ASD. Keeping this in mind, a possible theoretical explanation could be a concurrence of under connectivity and overconnectivity between cortical areas and cerebellum. This suggestion seems to be supported by findings from a study that, for the first time, explicitly assessed cortico-cerebellar connectivity in ASD (58). Another explication of the partly conflicting reports may be the developmental changes in functional connectivity (63). Theoretically, this opinion is based on the account of ASD as a "developmental disconnection syndrome," first proposed by Geschwind and Levitt, and more recently, by Wang et al. (36, 64). Given the developmental nature of the disorder, the connectivity abnormalities in ASD could vary in direction and in degrees of alteration through different stages of development as a result of neural plasticity. This hypothesis has received empirical support from diffusion imaging studies (65), resting-state studies using fMRI (66), and near-infrared spectroscopy (67). Abnormal developmental trajectories in ASD have been also found for the cortico-cerebellar connectivity (56, 60), as discussed above. Cross-sectional and longitudinal studies are warranted to control for the impact of studies' differences in age ranges of participants on findings. In order to better understand possible developmental abnormalities of cortico-cerebellum connectivity, animal models can also provide useful insights into how a damage in cortico-cerebellar connections at a specific age could result in abnormal autistic-like behaviors (68).

Another area of concern raised by the evidence reviewed here is the lack of a specific relationship between connectivity and behavioral/diagnostic measures of ASD. This might be due, at least in part, to the well-known heterogeneity of people with ASD. Thus, with respect to the aim of our work, it is not possible at this stage to draw a direct link between the disruption of a specific cerebro-cerebellar circuit and a restricted behavioral phenotype of patients. Future research could overcome this limitation by including subsets of patients defined on the basis of different quantifiable measures of ASD phenotype, such as motor impairments, stereotyped behaviors, or language difficulties, in order to understand the relationship between these "proxy markers" of the disorder and the cortico-cerebellar connectivity. Within this context, more neuroimaging observations are also needed to localize ASD abnormalities in connectivity to specific areas of the cerebellum. To do this, it could be useful to couple both structural and functional imaging with experimental neurobehavioral paradigms that encompass the role of the cerebellum in movement, language, and social cognition.

AUTHOR CONTRIBUTIONS

AC and PB conceived, designed, acquired background material, and drafted this work; GD, SBC, MN, and FA interpreted the background material, critically revised, and approved the final version of and agreed to be accountable for this work.

FUNDING

This work was supported by grant from the Italian Ministry of Health to Prof. Brambilla (Ricerca Corrente 2015, VirtAut) and to Crippa (GR-2011-02348929).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 19 April 2016
doi: 10.3389/fpsyt.2016.00069

Understanding Suicidal Behavior: The Contribution of Recent Resting-State fMRI Techniques

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Keywords: suicidal behavior, resting state, rsfMRI, functional deficits, brain networks

INTRODUCTION: SUICIDAL BEHAVIOR AND RESTING-STATE fMRI TECHNIQUES

Suicidal behavior is a relevant and multifaceted public health issue and is commonly associated with a significant disability and psychosocial impairment. To date, no available biomarkers are able to predict which subjects will develop suicide over time, and this is hardly surprising given the number of factors that have been hypothesized to modulate suicide risk based on the current literature (1).

In the effort to solve this shortcoming, a possible approach is represented by the search of those patterns of brain activation that are associated with suicidal behavior and may be identified using functional neuroimaging techniques. To date, the most commonly used functional neuroimaging technique is represented by functional magnetic resonance imaging (fMRI). fMRI may detect the local changes in the relative concentrations of oxy- and deoxy-hemoglobin, induced by local metabolic demand [i.e., it measures the so-called blood–oxygen level-dependent (BOLD) signals] (2). fMRI data can be also acquired while the imaged subject is performing a given task (i.e., task-dependent fMRI) or at rest (resting-state fMRI – rsfMRI).

There are studies showing aberrant neural activity patterns in suicide attempters that were carried out using task-based BOLD fMRI (3). Indeed, task-based fMRI has been used to probe the neural substrates of specific cognitive and emotional intermediate phenotype of suicide, such as error monitoring (4) and decision-making (5), but task-based fMRI is inherently limited by the need of active collaboration by the scanned subject as well as by the nature of the task during fMRI data acquisition. fMRI data can be also acquired while the subject is not performing any task – i.e., at rest (rsfMRI) – to evaluate which brain regions present same patterns of activation over time that are supposed to represent a valid surrogate marker of functional connectivity between different gray matter areas and over the whole brain (6).

Compared with task-based fMRI, rsfMRI is not dependent on subject collaboration (except for the requirement to lay in the scanner as much as possible), thus increasing its inter-subject and intra-subject reproducibility. Moreover, rsfMRI allows to explore the resting-state brain networks, in particular, the default mode network (DMN), that have been reported to be altered in several psychopathological conditions and may be not easily investigated using the commonly available task-based fMRI (7, 8). Finally, as rsfMRI data can be analyzed over the whole brain, they do not require to have an *a priori* hypothesis regarding the involvement of specific brain regions.

OPEN ACCESS

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *10 February 2016*
Accepted: *06 April 2016*
Published: *19 April 2016*

Citation:
Serafini G, Pardini M, Pompili M, Girardi P and Amore M (2016) Understanding Suicidal Behavior: The Contribution of Recent Resting-State fMRI Techniques. Front. Psychiatry 7:69. doi: 10.3389/fpsyt.2016.00069

CAN rsfMRI INFORM ABOUT SUICIDAL BEHAVIOR?

In order to perform a critical overview of the existing studies about the main topic, a reference search was carried out across the Medline and ScienceDirect databases (January 1980 and February 2016). The search used the following terms: "Resting-state fMRI" OR "Resting-state functional magnetic resonance imaging" OR "rsfMRI techniques" AND "Suicid*" (including suicidal behavior OR suicide ideation OR suicidal thoughts OR deliberate self-harm OR suicidal attempt). In addition, the reference lists of all papers identified were reviewed, and imaging evidence investigating suicidality as a secondary emergence of disturbed experience of self in personality disorders have been also included.

Although fMRI may investigate brain activity both in resting conditions and during activation, in the present paper, we mainly focused on brain imaging in resting conditions estimating regional brain activity when environmental activation is standardized. fMRI studies that investigated depressed patients pointed to the possible role of a host of different regions in this complex construct. Interestingly, all these brain areas have been also shown to play a role in different psychopathological domains such as modulation of physiological responses to emotions, emotional dysregulation, and self-processing, which in turn are also supposed to play a role in the emergence of suicide behavior (3, 5). As reviewed by Desmyter and colleagues (9), the reduced perfusion of the prefrontal cortex in suicidal patients is a commonly observed finding in functional neuroimaging resting conditions.

Indeed, the search for the neural bases underlying the cognitive and emotional intermediate phenotypes may reveal interesting neurocognitive constructs concerning suicidality. Cao et al. (10), for example, aimed to explore changes in neural circuit organization associated with suicidal behavior and proposed that disruptions in fronto-limbic or fronto-parietal–cerebellar pathways may lead to poor executive functioning, lack of impulse control, cognitive inflexibility, and impaired decision-making in suicidal young adults.

Very recently, Northoff (11) reported that depressive symptoms may be interpreted as spatiotemporal disturbances of the resting-state activity and its spatiotemporal structure according to the general assumption that brain resting-state activity may be defined in a functional/physiological manner rather than anatomically/structurally. Based on this suggestion, ruminations and enhanced self-focus in depressed patients are referred to abnormal spatial organization of resting-state activity, whereas anhedonia and suicidal ideation may be associated with increased focus on the past and enhanced past-focus as basic temporal disturbances of the resting state. Aiming to investigate the neural correlates of suicide thoughts, fMRI during presentation of autobiographical memories in depressed patients who recently attempted suicide has been also carried out. A deactivation of frontal cortical areas has been observed in suicidal episodes (mental pain plus suicide action), whereas an increased neural activity in the medial prefrontal, the anterior cingulate cortex, and the hippocampus occurred during the recall of the suicide action compared to mental pain (12). The authors suggested that suicidal mode is a state-dependent phenomenon that can be triggered by a specific stimulus and it may possess the quality of a traumatic state.

There are studies that indirectly addressed suicidal behavior using rsfMRI techniques [e.g., they mainly investigated relevant predictors of suicidal behavior such as hopelessness (13, 14)], and provided useful information about suicidality. Hopelessness is a powerful and informative psychological construct about suicidal behavior and addressed three major constructs: feelings regarding the future, loss of motivation, and expectations (15).

Interestingly, Northoff and colleagues (16) suggested that hopelessness and self-related processing were associated with higher resting-state neural activity in the DMN. Grimm and colleagues (17) aimed to investigate whether self-related emotional judgment may induce reduced negative BOLD responses (NBRs) in DMN regions of depressed patients. Reduced NBRs in the anterior regions of the DMN associated with abnormally increased self-focus together with ruminations, self-blame, abnormal coupling of the self to negative emotions, and enhanced attention to the own self were found among depressed patients relative to healthy individuals (18). Interestingly, higher self-relatedness of negative stimuli was also associated with hopelessness measured using the Beck Hopelessness Scale. This is in line with the observation that, clinically depressed patients usually present alterations in anticipating the future, but they also show increased retrieving and ruminating about past events (19). The study of Grimm and colleagues (17) postulated the existence of a dysregulated balance between anterior and posterior medial regions of NBRs during self-related judgment that may suggest a shift in the functional balance between anticipation and retrieval, or future and past.

Figure 1 showed the potential of rsfMRI techniques to inform about vulnerability to suicidal behavior. We mainly focused on self-relatedness of negative stimuli that, according to Grimm and colleagues (17), are predominantly related to reduced NBRs in the anterior regions of the DMN and increased vulnerability to suicidal behavior, whereas we omitted to mention the role of motivational and consummatory anhedonia that are presumably associated with reward network dysfunctions [for more details about this topic, see the recent review of Lener and Iosifescu (20)].

Further additional details need to be discussed in this regard. Recently, Johnston and colleagues (21) also reported an abnormally increased hippocampal activity during loss events, which has been associated with self-reported depression and hopelessness in a sample of 20 patients with treatment-resistant MDD and 21 healthy controls. According to the assumptions of Deakin (22), the authors hypothesized that the failure to deactivate the hippocampus during loss events is mediated by the abnormal median raphe nucleus functioning, which is normally implicated in mediating resilience and is usually able to inhibit rehearsal of aversive memories. This is also confirmed by the "dorsal raphe nucleus-periaqueductal gray-amygdala-striatum" hypothesis about depressive illness, which has been initially postulated by Deakin and Graeff (23). This theory suggested that major

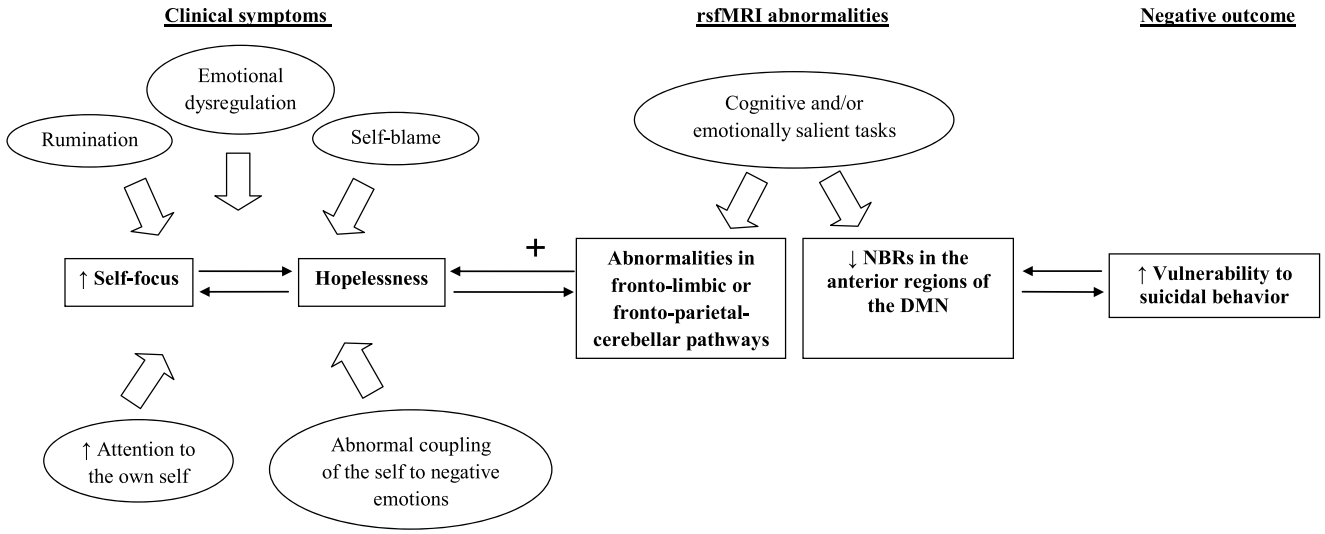

FIGURE 1 | **The relationship between fMRI abnormalities and vulnerability to suicidal behavior**. Note: default mode network (DMN), negative blood oxygenation level-dependent responses (NBRs), resting-state functional magnetic resonance imaging (rsfMRI).

depression is a complex condition including anxiety symptoms associated with the overactivity of dorsal raphe nucleus and its projections to the amygdala, helplessness related to the overactivity of periaqueductal gray, anhedonia associated with the overactivity of caudate/striatum as well as ruminations related to the underactivity of median raphe nucleus and its projections to the hippocampus (23).

Finally, there are also imaging evidence that investigated suicidality as a secondary emergence of disturbed experience of self in subjects with personality disorders. For example, borderline personality disorders (BPD) may be significantly associated with suicidal behavior as subjects with this psychiatric condition frequently exhibit recurrent suicidal threats, gestures, behavior, or self-mutilation (9, 24). In particular, Oumaya and colleagues (24) reported that self-mutilating suicide attempters may be more likely to experience feelings of depression and hopelessness, impulsivity, and affective instability, but they may also underestimate the lethality of suicidal behavior. Xu and colleagues (25), in the effort to identify an objective test to assist the clinical diagnosis of BPD, analyzed a sample of 21 patients with BPD and 10 healthy controls and reported that the most discriminating deficits between the two groups were located in the left medial orbitofrontal cortex, the left thalamus, and the right rostral anterior cingulate cortex. Other researchers (26) used rsfMRI to investigate changes in functional connectivity in a sample of 32 subjects with antisocial personality disorder (APD) and 35 healthy controls. Both functional and structural deficits of the precuneus, the superior parietal gyrus, and the cerebellum that may underlie the low arousal, high impulsivity, lack of conscience, cold-bloodedness, and decision-making deficits have been reported in subjects with APD when compared to healthy controls exposing them to a greater risk for suicide.

MAIN SHORTCOMINGS AND FUTURE PERSPECTIVES

Overall, rsfMRI studies suggest the potential to identify functional intermediate phenotypes that may provide interesting information about suicide risk identification.

However, rsfMRI studies need to be considered in the light of several limitations. First, based on the current knowledge about this topic, it is unclear whether the reported abnormalities represent risk markers for suicide or are directly related to the course of illness as a result of disease processes. Unfortunately, a comprehensive understanding of the altered mechanisms involved at the level of dysfunctional brain networks in subjects at risk for suicide is still lacking.

In addition, rsfMRI studies are performed using inferences at the group level according to traditional statistical hypotheses and the predictive potential of the patterns may be unlikely generalized when applying to new individuals (25). Moreover, existing rsfMRI studies usually include relatively small and clinically heterogeneous samples (e.g., predominantly suicidal young adults) that may have seriously limited their statistical power. Furthermore, subject motion during the scan may significantly influence rsfMRI findings, although several methods have been proposed including approaches to reduce the impact of motion artifacts. The potential effect of psychoactive medications in rsfMRI studies cannot be ruled out as well. Almost all of the patients who have been recruited by the existing studies were on psychotropic medications due to ethical considerations. Studies may also lack detailed information regarding medication doses or the duration of treatment.

In conclusion, elucidating the functional deficits associated with specific network disturbances may help to clarify the pathophysiological mechanisms underlying suicidal

behavior and assist in identifying high-risk individuals in clinical practice. However, further studies involving larger samples of non-medicated individuals are needed to investigate the nature of the relationship between rsfMRI data and suicidal behavior. These additional researches could focus on examining at-risk individuals and relatives of affected subjects or shifts in brain networks before and after the emergence of suicidal ideation/attempts in order to clarify specific causal pathways related to the observed network abnormalities. The utilization of multivariate algorithms to obtain information from multiple domains, such as neural networks, genetic and epigenetic markers, self-report instruments, clinical interviews, and support diagnosis and treatment selection, are recommended as well.

AUTHOR CONTRIBUTIONS

GS conceived, designed, and drafted the present manuscript. MPa participated in the concept and helps in reviewing the current literature about the main topic. MPo critically reviewed the paper. MA and PG provided the intellectual impetuous and supervised the writing of the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JW and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Psychiatry

REVIEW
published: 18 May 2016
doi: 10.3389/fpsyt.2016.00082

Effect of Pharmacological Interventions on the Fronto-Cingulo-Parietal Cognitive Control Network in Psychiatric Disorders: A Transdiagnostic Systematic Review of fMRI Studies

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OPEN ACCESS

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *15 January 2016*
Accepted: *26 April 2016*
Published: *18 May 2016*

Citation:
van Amelsvoort T and Hernaus D (2016) Effect of Pharmacological Interventions on the Fronto-Cingulo-Parietal Cognitive Control Network in Psychiatric Disorders: A Transdiagnostic Systematic Review of fMRI Studies. Front. Psychiatry 7:82. doi: 10.3389/fpsyt.2016.00082

Executive function deficits, such as working memory, decision-making, and attention problems, are a common feature of several psychiatric disorders for which no satisfactory treatment exists. Here, we transdiagnostically investigate the effects of pharmacological interventions (other than methylphenidate) on the fronto-cingulo-parietal cognitive control network, in order to identify functional brain markers for future procognitive pharmacological interventions. Twenty-nine manuscripts investigated the effect of pharmacological treatment on executive function-related brain correlates in psychotic disorders (n = 11), depression (n = 4), bipolar disorder (n = 4), ADHD (n = 4), OCD (n = 2), smoking dependence (n = 2), alcohol dependence (n = 1), and pathological gambling (n = 1). In terms of impact on the fronto-cingulo-parietal network, the preliminary evidence for catechol-*O*-methyl-transferase inhibitors, nicotinic receptor agonists, and atomoxetine was relatively consistent, the data for atypical antipsychotics and anticonvulsants moderate, and interpretation of the data for antidepressants was hampered by the employed study designs. Increased activity in task-relevant areas and decreased activity in task-irrelevant areas were the most common transdiagnostic effects of pharmacological treatment. These markers showed good positive and moderate negative predictive value. It is concluded that fronto-cingulo-parietal activity changes can serve as a marker for future procognitive interventions. Future recommendations include the use of randomized double-blind designs and selective cholinergic and glutamatergic compounds.

Keywords: psychopharmacology, fMRI, psychiatric disorders, attention, cognition, prefrontal cortex, executive functioning, treatment

INTRODUCTION

How are pharmacological interventions for psychiatric disorders related to changes in functional brain correlates of executive functions? Impairments in executive functions, such as working memory, decision-making, planning, and attention, are a common feature of several psychiatric disorders. Extensive evidence in depression (1, 2), schizophrenia (SCZ) and psychosis (3, 4), bipolar disorder (5, 6), obsessive–compulsive disorder (OCD) (7, 8), substance dependence (9, 10), anxiety (11), autism spectrum disorders (12, 13), and attention-deficit/hyperactivity disorder (ADHD) (14, 15) suggests consistent impairments on a broad range of neuropsychological tests. For many of these disorders, there is compelling evidence that executive function deficits may be present before illness onset (16–18) and often persist beyond the acute phase of the disease (9, 19–21). With the exception of ADHD, there currently exists no successful pharmacological treatment for executive function deficits in psychiatric disorders.

The fact that assessments of executive functions in psychiatric disorders predict relapse/remission (9, 22, 23), functional outcome (24, 25), and in some cases, treatment response (26, 27) suggests that it is a core transdiagnostic symptom domain that requires adequate treatment. Recent reviews have suggested that increasing patient functioning and outcome may be achieved by boosting executive functions (28, 29), further increasing attractiveness of this symptom domain as a treatment target.

Then, do the available pharmacological interventions for the treatment of psychiatric disorders modulate executive function deficits? Based on the available literature, especially the dopamine- and noradrenaline-increasing effects of methylphenidate (MPH) have been consistently associated with normalizing effects in ADHD (30, 31) and procognitive effects in healthy volunteers (32). And, many other pharmacological agents with glutamatergic [e.g., memantine (33)], cholinergic [e.g., rivastigmine (33)], dopaminergic [e.g., modafinil (34) and atomoxetine (35)], and noradrenergic [e.g., atomoxetine (35)] properties have also been shown to modulate executive functions. Moreover, while not the *primary aim* of these agents, there is evidence for a modest improvement in some executive function domains for atypical antipsychotics (36), likely related to their dopamine- and serotonin-modulating properties.

It may be the case that pharmacological agents for psychiatric disorders, *which may or may not have the primary aim to modulate executive functions*, at least partly impact common substrates. Although executive functions are underlain by widely distributed networks, one brain network consistently associated with executive functions is the fronto-cingulo-parietal cognitive control network (37). Essential hubs in the fronto-cingulo-parietal network have consistently been associated with executive function domains such as the anterior cingulate cortex with cognitive control (38), dorsolateral prefrontal cortex (DLPFC) with working memory (37, 39), inferior frontal gyrus (IFG) and (pre-)supplementary motor area (SMA) with response inhibition (40–42), and the parietal lobules with visual attention and attention control (43, 44). As such, the fronto-cingulo-parietal network is ideally suited as a reference network, which can be used to evaluate the effect of pharmacological agents on executive function-related brain networks.

While especially the effect of MPH on cognitive control networks has been critically evaluated in relation to its pharmacological mechanism (30, 31), the aim of the *current review* was to systematically review the evidence for other available pharmacological interventions in a transdiagnostic fashion. This includes not only pharmacological agents with demonstrated procognitive effects but also agents that are not primarily used to ameliorate executive function deficits, such as antidepressants or antipsychotics. Relating plausible mechanisms of action to the effect of pharmacological interventions on functional brain correlates of executive functions could assist in further (I) validating the therapeutical effects of these agents and (II) elucidating brain mechanisms that could be targeted by future procognitive agents.

The use of functional magnetic resonance imaging (fMRI) to investigate brain correlates of executive functions is well established (45). More recently, this method has increasingly been used to evaluate the effects of pharmacological agents on brain function (46, 47). The strength of pharmacological fMRI is its ability to quantify activity changes in functional brain networks related to direct or downstream consequences of the pharmacological intervention. This enables the investigation of *common and distinct* drug effects on functional brain networks.

In this transdiagnostic systematic review, we aim to provide an overview of the effects of pharmacological interventions (other than MPH) on the fronto-cingulo-parietal cognitive control network in psychiatric disorders and to relate these to plausible neuropharmacological mechanisms. Using recent meta-analyses, we start off with a brief definition of the fronto-cingulo-parietal network. Next, we specifically evaluate original studies employing *strictly* executive functioning fMRI paradigms before treatment and after stable therapeutically efficacious dosing (monotherapy or adjunctive) had been implemented. We conclude with common transdiagnostic effects of pharmacological agents on the fronto-cingulo-parietal network, which could serve as markers for future procognitive interventions.

METHODS

PubMed was searched for studies published before October 23, 2015 using the initial Boolean phrase: ("fMRI" OR "functional magnetic resonance imaging") AND ("cognition" OR "working memory" OR "attention" OR "decision-making" or "verbal learning" or "vigilance" or "processing speed" or "reasoning" or "problem solving" or "social cognition" or "verbal memory" or "visual learning" or "visual memory") AND ("treatment") AND ("pharmacology"). We followed up this initial search with a number of targeted searches in psychiatric disorders. To these aims, we replaced ("treatment") AND ("pharmacology") with ("pharmacology" OR "treatment") AND (i) ("depression" OR "MDD"), (ii) ("schizophrenia" OR "psychosis"), (iii) ("bipolar" OR "mania" OR "cyclothymia" OR "rapid cycling"), (iv) ("substance dependence" OR "addiction" OR "substance abuse" OR "alcoholism"), (v) ("Tourette syndrome" OR "Tourette" OR "tic"), (vi) ("borderline" OR "personality disorder"), (vii) ("autism" OR "pervasive developmental disorder" OR "Asperger"), (viii) ("obsessive compulsive

disorder" OR "OCD" OR "impulse control"), (ix) ("PTSD" or "post traumatic stress disorder"), and (x) ("anxiety" OR "fear" OR "phobia"). Titles and abstracts of all results were screened. Cross-referencing was performed on all included manuscripts and relevant reviews. Given the high number of recent meta-analyses and systematic reviews on the subject (30, 31, 48), we did not systematically review results of MPH treatment in psychiatric disorders. Treatments other than MPH in ADHD were included in the review if they met criteria.

Manuscripts were only considered if

(i) they were published in a peer-reviewed journal.
(ii) they were written in the English language.
(iii) they used the same fMRI paradigm at baseline and follow-up.
(iv) they reported group-level statistics; case studies were not included.
(v) pharmacological agents were specified, and results of the medicated group were reported (e.g., manuscripts combining samples of non-pharmacologically and pharmacologically treated patients were excluded).
(vi) the entire sample of patients was drug-free (in the case of monotherapy) or on stable monotherapy (in the case of adjunctive therapy) at baseline (washout allowed if necessary) and were stably and actively on (adjunctive) medication (no washout) during follow-up session(s). Concretely, "stably on medication" refers to repeated administration (>1; single dosing studies excluded) of the same efficacious drug dose.
(vii) they used fMRI paradigms that *only* measured aspects of executive functions. Tasks with stressful, painful, emotional, and/or rewarded components were excluded.
(viii) participants had a diagnosis of a psychiatric disorder according to DSM-IV criteria. Neurological disorders, such as stroke, dementia, and Parkinson's disease, were excluded.

Definition of and Rationale for the Cognitive Control Network as a Reference Network

The functional brain networks underlying higher cognitive and attention functions are widespread and complex with among others demonstrated cerebellar (49), occipital cortex (50, 51), striatal (52), and frontal cortical (39) involvement. In order to provide a clear delineation of the topic and facilitate the use of a reference network, we decided to review the effect of pharmacological agents on the fronto-cingulo-parietal cognitive control network. The cognitive control network has been hypothesized to play an essential role in orchestrating higher order behavior such as decision-making, action selection, and working memory (53). A comprehensive meta-analysis by Niendam et al. (37) demonstrated recurrent activity of a fronto-cingulo-parital cognitive control network during paradigms that assess working memory, response inhibition, behavioral flexibility, and other higher order skills (37). These results are in line with previous meta-analyses on functional brain networks underlying working memory, response inhibition, and selective attention, specifically and consistently revealing ACC, DLPFC, and superior and inferior parietal lobule (IPL) activity (41, 54–56). Therefore, the reported results in this manuscript (**Table 1**) include observed changes in parietal cortex (superior and IPL), insula, ACC, and frontal cortical areas, including DLPFC, ventrolateral PFC (VLPFC), and orbitofrontal cortex (OFC). In the discussion, these results will be linked to other notable findings of the available studies.

RESULTS

The review was carried out according to PRISM (57) guidelines. The literature search in PubMed yielded 586 unique hits, of which 557 were excluded because they did *not* (i) utilize a pharmacological intervention or used MPH (38.2%), (ii) recruit patient populations (28.5%), (iii) employ a longitudinal fMRI design (17.8%), (iv) utilize a repeated dosing scheme (8.3%), (v) employ strictly cognitive tasks (4.4%), or (vi) were not written in the English language (2.8%). Thus, 29 manuscripts were included in this review, of which 26 used unique samples. In total, 431 individuals were scanned while medication free or on stable monotherapy at baseline and on monotherapy or adjunctive treatment at follow-up, in addition to placebo-treated patients and healthy volunteers.

Study designs, tasks, sample size, medication distribution, and main findings of the included studies are reported in **Table 1**. If available, results regarding (i) changes over time in patients vs. controls and (ii) patients vs. controls at follow-up were reported. Else, results regarding (i) change over time in patients and (ii) patients at follow-up vs. controls at follow-up, or (iii) patients at follow-up vs. controls at baseline were reported.

Acetylcholinesterase Inhibitors

Three studies (two unique samples) investigated the effect of adjunctive actylcholinesterase inhibitors on executive function-related brain correlates before and after treatment. All studies were conducted in SCZ, and a total of 17 patients who were on stable antipsychotic medication were scanned before and after adjunctive treatment with actylcholinesterase inhibitors. Six patients were administered donepezil; the remaining 11 patients received rivastigmine.

Psychotic Disorders

None of the reported studies observed significant changes in task performance between placebo and medication sessions or between groups.

In a crossover design, Nahas et al. (58) investigated the effect of 12-week adjunctive donepezil treatment on verbal fluency-related brain activity. On donepezil relative to placebo, participants displayed increased left IFG and insula activity.

Aasen et al. (59) investigated brain activity during a number detection task in a 12-week rivastigmine trial. At follow-up and relative to placebo-treated patients, rivastigmine-treated patients did not show changes in fronto-cingulo-parietal activity. On the *n*-back task, which assesses selective attention and working memory, Kumari et al. (60) found a smaller increase in right superior frontal gyrus (SFG) activity from baseline to follow-up in the same sample of rivastigmine-treated patients, relative to placebo-treated patients.

TABLE 1 | Overview of the effect of pharmacological agents on the fronto-cingulo-parietal cognitive control network.

Reference	Diagnosis	*N* (treated)	*N* (PLC arm)	*N* (CTRL arm)	Study design	Treatment	Duration	Task	Main behavioral results	Main fMRI results	Timepoint and/or group comparisons	Task contrast
Acetylcholinesterase inhibitors												
Nahas et al. (58)	SCZ (atypical antipsychotics)	6	–	–	Randomized double-blind PLC-controlled crossover design	Donepezil adjunctive treatment	12 weeks	Covert verbal fluency task	No changes in task performance over time	On donepezil relative to PLC, ↑ left IFG and left insula activity	Patients (donepezil vs. PLC)	Word generation vs. rest
Aasen et al. (59)[A]	SCZ (antipsychotics)	11	9	–	Randomized double-blind PLC-controlled trial	Rivastigmine adjunctive treatment	12 weeks	Number detection task	No (between-group) differences in task performance (over time)	–	–	–
Kumari et al. (60)[A]	SCZ (atypical antipsychotics)	11	10	–	Randomized double-blind PLC-controlled trial	Rivastigmine adjunctive treatment	12 weeks	*n*-back	No (between-group) differences in task performance (over time)	Over time and relative to PLC patients at T1, no ↑ in right SFG activity	Rivastigmine (T0, T1) vs. PLC (T0, T1)	1-back vs. rest
Anticonvulsants												
Pavuluri et al. (61)	BD (pediatric; mania or mixed)	13	–	13; T0, T1	Open-label trial	Typical antipsychotics (weeks 1–4); lamotrigine (weeks 1–14)	14 weeks	Go/no go	Overall relative to CTRL, ↓ accuracy on No Go trials	Over time and relative to CTRL, greater ↑ in left PFC and right MFG activity	Lamotrigine (T0–T1) vs. CTRL (T0–T1)	Go vs. No Go
									Over time and similar to CTRL, ↑ accuracy on Go trials	At T1 relative to CTRL, ↑ left M1* activity	Lamotrigine (T1) vs. CTRL (T0)	Go vs. No Go
Pavuluri et al. (62)[C]	BD (pediatric; mania or mixed)	11	–	14; T0, T1	Randomized double-blind trial	Divalproex	6 weeks	Go/no go	At T0 relative to CTRL, ↓ discrimination sensitivity; comparable to CTRL at T1[E]	Over time relative to CTRL, greater ↑ in left subgenual ACC and left insula FC in affective network	Divalproex (T0–T1) vs. CTRL (T0–T1)	During response inhibition
Schneider et al. (63)	BD (pediatric; mania or mixed)	10	–	9; T0	Open-label trial	Carbamazepine	8 weeks	CPT – identical pairs	At T0 and T1 relative to CTRL at T0, ↓ accuracy	Over time, ↑ anterior PFC activity; n.s. at T1 relative to CTRL at T0	Carbamazepine (T0–T1); carbamazepine (T1) vs. CTRL (T0)	1-back vs. "1" detection
Antidepressants: selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors												
Walsh et al. (64)	Major depression	20	–	20; T0–T2	Open-label trial	Fluoxetine	8 weeks	*n*-back	Over time relative to CTRL, ↑ 3-back accuracy; At T0–T2 relative to CTRL, ↑ reaction times	–	–	–
Aizenstein et al. (65)	Late-life depression	13	–	13; T0	Open-label trial	Paroxetine	12 weeks	Spatial incompatibility task	At T1 relative to CTRL at T0, ↓ accuracy	Over time, ↑ right DLPFC activity; at T1 relative to CTRL at T0, ↓ left DLPFC activity	Paroxetine (T0 vs. T1); paroxetine (T1) vs. CTRL (T0)	Contralateral vs. baseline, ipsilateral vs. baseline
Wagner et al. (66)[D]	Major depression	12	–	20; T0	Open-label trial	Citalopram	6 weeks	Stroop color-word task	Over time, greater ↓ in reaction time for incongruent trials, relative to congruent trials[F]	Over time, ↓ right VLPFC, SMA, IPL, and SPL activity	Citalopram (T0 vs. T1); citalopram (T0, T1) vs. reboxetine (T0, T1)	During incongruent condition

(Continued)

TABLE 1 | **Continued**

Reference	Diagnosis	*N* (treated)	*N* (PLC arm)	*N* (CTRL arm)	Study design	Treatment	Duration	Task	Main behavioral results	Main fMRI results	Timepoint and/or group comparisons	Task contrast
										At T1 relative to CTRL at T0, n.s. group differences[F]	Patients (T1) vs. CTRL (T0)	During incongruent condition
Gyurak et al. (67)	Major depression	79	–	34; T0, T1	Randomized open-label trial	Escitalopram (n = 26), Sertraline (n = 27), Venlafaxine ER (n = 26)	8 weeks	Go/No Go	–	Over time, remitters and CTRL show ↓ DLPFC activity; over time, no change in hypo-DLPFC activity of non-remitters	CTRL (T0 vs. T1); remitted (T0, T1) vs. non-remitted (T0, T1)	Go vs. No Go
										At T0 and T1, n.s. group differences in IPL activity between SSRI remitters and CTRL	Remitted (T0/T1) vs. CTRL (T0/T1)	Go vs. No Go
										At T0, ↓ IPL activity in SNRI remitters than CTRL and SSRI remitters	Treatment (SSSRI, SNRI) vs. status (remitted, non-remitted, CTRL) vs. time (T0, T1)	Go vs. No Go
										At T1, ↓ IPL activity in SNRI remitters than in CTRL		
van der Wee et al. (68)	OCD	14	–	–	Randomized double-blind trial	Paroxetine (n = 9), venlafaxine (n = 5)	12 weeks	*n*-back	Over time, responders, but not non-responders, ↑ accuracy	Over time and relative to non-responders, ↓ mean fronto-cingulo-parietal[G] activity	Remitted (T0, T1) vs. non-remitted (T0, T1)	2-back vs. 0-back, 1-back vs. 0-back
Han et al. (69)	OCD	10	–	20; T0	Open-label trial	Escitalopram (n = 9), fluoxetine (n = 1)	16 weeks	Task-switching paradigm	At T0 and T1 relative to CTRL, ↓ accuracy. Over time, ↓ task-switching costs (RT)	Over time, ↑ right ACC, right insula, right PCG, and right PC activity	Patients (T0 vs. T1)	Task switching vs. task-repeat
										At T1 relative to CTRL at T0, ↓ DLPFC†, DMPFC†, right MFC† and PC† activity, and ↑ left insula* activity	Patients (T1) vs. CTRL (T0)	Task switching vs. task-repeat
Atypical antipsychotics												
Pavuluri et al. (62)[C]	BD (pediatric; mania or mixed)	11	–	14; T0 and T1	Randomized double-blind trial	Risperidone	6 weeks	Go/no go	At T0 relative to CTRL, ↓ discrimination sensitivity; comparable to CTRL at T1[E]	Over time relative to CTRL, greater ↑ in insular FC in affective network	Risperidone (T0–T1) vs. CTRL (T0–T1)	During response inhibition
Schneider et al. (63)	BD (pediatric; mania or mixed)	10	7	10; T0	Randomized double-blind PLC-controlled trial	Ziprasidone	4 weeks	CPT – identical pairs	No between-group differences in task performance (over time)	Over time relative to PLC patients, greater ↑ in right VLPFC/OFC activity	Ziprasidone (T0–T2) vs. PLC (T0–T2)	1-back vs. "1" detection

(Continued)

TABLE 1 | **Continued**

Reference	Diagnosis	*N* (treated)	*N* (PLC arm)	*N* (CTRL arm)	Study design	Treatment	Duration	Task	Main behavioral results	Main fMRI results	Timepoint and/or group comparisons	Task contrast
										At T1 and T2 compared to CTRL at T0, n.s. group differences in VLPFC/OFC activity	Patients (T0/T1/T2) vs. CTRL (T0)	1-back vs. "1" detection
Snitz et al. (70)	FEP	11	–	16; T0 and T1	Open-label trial	Risperidone (n = 7); olanzapine (n = 3); quetiapine (n = 1)	4 weeks	Spatial incompatibility task	At T0 and T1 relative to CTRL, ↑ reaction times	Over time, ↑ ACC, but not DLPFC, activity	Patients (T0 vs. T1)	Contralateral vs. baseline, ipsilateral vs. baseline
										At T1 relative to CTRL, n.s. group differences in DLPFC and ACC activity	Patients (T1) vs. CTRL (T1)	Contralateral vs. baseline, ipsilateral vs. baseline
Meisenzahl et al. (71)	SCZ	12	–	12; T0	Open-label trial	Quetiapine	12 weeks	n-back (degraded and non-degraded)	No (between-group) differences in task performance (over time)	Over time, ↑ left VLPFC (non-degraded) and right precuneus (degraded) activity	Quetiapine (T0 vs. T1)	2-back vs. 0-back
Keedy et al. (72)	FEP	9	–	9; T0 and T1	Open-label trial	Risperidone (n = 6), ziprasidone (n = 1), haloperidol (n = 2)	4–6 weeks	Visual attention task	–	Over time, ↑ left FEF activity and ↓ IPS and VMPFC activity; n.s. at T1 relative to CTRL	Patients (T0 vs. T1); Patients (T1) vs. CTRL (T1)	Prosaccade vs. fixation
										At T1 relative to CTRL, ↓ supramarginal gyri*, insula*, DLPFC*, SEF† and ACC activity	Patients (T0 vs. T1); Patients (T1) vs. CTRL (T1)	Prosaccade vs. fixation
Ikuta et al. (74)	FEP	14	–	14; T0 and T1	Randomized double-blind trial	Risperidone or aripiprazole (n not specified)	12 weeks	Multi-source inference task	Over time, ↑ response accuracy; at T1 relative to CTRL, ↓ accuracy	Over time, ↓ SFG activity; ↑ left SFG and rostral PFC activity	Patients (T0 vs. T1)	Interference vs. control
Keedy et al. (73)	FEP	14	–	12; T0 and T1	Open-label trial	Risperidone (n = 12), aripiprazole (n = 2)	4–6 weeks	Visual attention task	No (between-group) differences in prosaccade task performance (over time)	Over time, ↑ SEF, IPS and SPC activity; at T1 relative to CTRL, n.s. group differences	Patients (T0 vs. T1); Patients (T1) vs. CTRL (T1)	Prosaccade vs. fixation
									Over time, ↑ anticipatory saccades during predictive saccade task; at T1 relative to CTRL, n.s. differences	Over time, ↑ left IPS activity and ↓ DLPFC activity; n.s. group differences	Patients (T0 vs. T1); Patients (T1) vs. CTRL (T1)	Predictive saccade vs. fixation

(Continued)

TABLE 1 | **Continued**

Reference	Diagnosis	*N* (treated)	*N* (PLC arm)	*N* (CTRL arm)	Study design	Treatment	Duration	Task	Main behavioral results	Main fMRI results	Timepoint and/or group comparisons	Task contrast
Benzodiazepines												
Wilcox et al. (75)	Alcohol use disorder; comorbid anxiety	7	–	9; T0	Open-label trial	Lorazepam plus disulfiram	5–7 days	Multimodal stroop task	Overall relative to CTRL at T0, ↑ reaction times	Over time, ↓ right IPL and insula deactivity	Lorazepam + disulfiram (T0 vs. T1)	Incongruent vs. congruent (Scan 1), incongruent + congruent (Scan 2)
COMT inhibitors												
Ashare et al. (76)	Smoking dependence (24-h abstinent)	20	–	–	Randomized double-blind PLC-controlled crossover design	Tolcapone	8 days	*n*-back	On tolcapone relative to PLC, ↑ accuracy	On tolcapone relative to PLC, ↑ VMPFC deactivity	Patients (tolcapone vs. PLC)	0 + 1 + 2 + 3 back vs. baseline
									On tolcapone relative to PLC, ↑ reaction times for Val/Val, ↓ reaction times for Val/Met	On tolcapone relative to PLC, ↓ MFG activity and ↑ VMPFC deactivity in Val/Val and ↑ MFG and right DLPFC activity in Val/Met	Patients (tolcapone, PLC) for genotype (Val/Val, Val/Met)	0 + 1 + 2 + 3 back vs. baseline
Grant et al. (77)	Pathological gambling	12	–	12; T0	Open-label trial	Tolcapone	8 weeks	Tower of London task	No overall between-group differences in task performance	Over time, ↑ fronto-cingulo-parietal^{H} activity; at T1, fronto-cingulo-parietal^{H} activity normalized to CTRL at T0	Tolcapone (T0 vs. T1); tolcapone (T1) vs. CTRL (T0)	Planning condition vs. counting condition
Nicotinic receptor agonists												
Tregellas et al. (79)[B]	SCZ (non-smoking; antipsychotics)	16	–	–	Randomized double-blind PLC-controlled crossover design	Varenicline	4 weeks	Visual attention task	–	–	–	–
Tregellas et al. (80)[B]	SCZ (non-smoking; antipsychotics)	16	–	–	Randomized double-blind PLC-controlled crossover design	DMXB-A	4 weeks	Visual attention task	–	On DMXB-A 150 and 75 mg relative to PLC, ↓ IPL and MFG DMN activity and ↑ precuneus DMN activity	Patients (150 mg vs. PLC; 75 mg vs. PLC)	During prosaccade and rest
Loughead et al. (78)	Smoking dependence (72-h abstinent)	22	–	–	Randomized double-blind PLC-controlled crossover design	DMXB-A	13 days	*n*-back	On varenicline relative to PLC, ↓ reaction times in highly dependent smokers, but not lowly dependent smokers	On varenicline relative to PLC, ↑ ACC and DLPFC activity;↓ PFC activity (peak in right SFG and left IFG)	Patients (varencline vs. PLC)	3-back vs. 0-back, 2-back vs. 0-back, 1-back vs. 0-back

(Continued)

TABLE 1 | **Continued**

Reference	Diagnosis	*N* (treated)	*N* (PLC arm)	*N* (CTRL arm)	Study design	Treatment	Duration	Task	Main behavioral results	Main fMRI results	Timepoint and/or group comparisons	Task contrast
Norepinephrine reuptake inhibitors												
Schulz et al. (81)	ADHD (pediatric)	16	–	–	Randomized double-blind trial	Atomoxetine; MPH comparison (*n* = 18)	6–8 weeks	Go/No Go	Over time and similar to MPH, ↑ accuracy on No Go trials	Over time and similar to MPH, ↓ M1 activity	Atomoxetine (T0–T1) vs. methylphenidate (T0–T1)	Go vs. No Go
									Over time and similar to MPH, ↓ reaction time and reaction time variability on Go trials	Over time and relative to MPH, ↑ right IFG, left ACC, left SMA, and PCG activity (MPH ↓ activity in these regions)	Atomoxetine (T0–T1) vs. methylphenidate (T0–T1)	Go vs. No Go
Bush et al. (82)	ADHD (adults)	11	10	–	Randomized trial	Atomoxetine; MPH comparison (*n* = 11)	6 weeks	Multi-source interference task	No differences in task performance (over time)	Over time, ↑ right DLPFC, left IPL, left SMA, and left insula activity	Atomoxetine (T0 vs. T1)	Interference vs. control
Chou et al. (83)	ADHD (pediatric)	22	–	20; T0	Randomized trial	Atomoxetine; MPH comparison (*n* = 20)	12 weeks	Stroop Counting Task	Over time and similar to MPH, ↓ reaction time during incongruent trials	Over time relative to MPH, greater ↑ in left dorsal ACC and DLPFC activity and smaller ↓ in left IFG activity	Atomoxetine (T0, T1) vs. methylphenidate (T0, T1)	Incongruent vs. congruent
Wagner et al. (66)[D]	Major depression	8	–	20; T0	Open-label trial	Reboxetine	6 weeks	Stroop color-word task	Over time, larger ↑ in reaction time for incongruent trials, relative to congruent trials[F]	–	–	–
Friedman et al. (84)	SCZ (atypical antipsychotics)	5	3	–	Randomized double-blind PLC-controlled design	Atomoxetine adjunctive treatment; PLC (*n* = 3)	8 weeks	*n*-back	–	At T1 relative to PLC patients, ↑ left DLPFC activity	Atomoxetine (T1) vs. PLC (T1)	2-back + 3-back vs. 0-back
$\alpha 2_A$ adrenergic receptor agonists												
Bedard et al. (85)	ADHD (pediatric)	12	13	–	Randomized double-blind PLC-controlled trial	Guanfacine	6–8 weeks	Go/No Go	No differences in task performance (over time)	Over time relative to PLC patients, n.s. differences	Guanfacine (T0, T1) vs. PLC (T0, T1)	Go vs. No Go

[*]Appeared; not present at T0, present at T1.

[†]Remained; present at T0 and T1.

↑, increased or higher; ↓, decreased or lower; T0, baseline; T1 and T2, follow-up; CTRL, healthy volunteers; PLC, placebo-treated; MPH, methylphenidate; FC, functional connectivity; DMN, default mode network. Psychiatric disorder: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; OCD, obsessive–compulsive disorder; FEP, first-episode psychosis; SCZ, schizophrenia.

Brain regions: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; FC, frontal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IPS, intraparietal sulcus; M1, primary motor area; MFC, medial frontal cortex; MFG, medial frontal gyrus; OFC, orbitofrontal cortex; PC, parietal cortex; PFC, prefrontal cortex; SEF, supplementary eye fields; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex.

[A,B]Identical sample. [C,D]Part of same investigation. [E,F]Significant effect/association in combined sample. [G]Consists of ACC, DLPFC, premotor cortex, and PC. [H]Consists of DLPFC, IPL, and frontopolar cortex.

Anticonvulsants

We identified three manuscripts investigating the effect of anticonvulsants on the functional brain correlates of executive functions. All studies were conducted in pediatric bipolar disorder (age <18 years). A total of 34 pediatric patients were scanned before and after treatment. Thirteen patients were treated with lamotrigine, 11 with divalproex, and 10 with carbamazepine.

Bipolar Disorder

Pavuluri et al. (61) reported that, on a response inhibition task, pediatric bipolar patients displayed poorer overall (i.e., average of baseline and follow-up) accuracy on No-Go trials than healthy volunteers. However, similar to healthy volunteers, performance accuracy on Go trials increased from baseline to follow-up. From baseline to follow-up and compared to healthy volunteers, bipolar patients showed greater increases in left PFC and right medial frontal gyrus activity. At follow-up relative to healthy volunteers, increased left motor cortex activity appeared.

Another study by Pavuluri and colleagues (62) investigated the effect of divalproex on response inhibition and related functional connectivity. When divalproex-treated patients were combined with a parallel arm of risperidone-treated patients (see Atypical Antipsychotic treatment in Bipolar Disorder), discrimination sensitivity during a Go/No-Go task at baseline was poorer in patients than in healthy volunteers, but seemed to have normalized at follow-up. From baseline to follow-up and compared to healthy volunteers, divalproex-treated patients showed a greater increase in left subgenual ACC and left insula functional connectivity in an affective network. Directly comparing the divalproex- and risperidone-treated patient group, the latter group showed a trend-significant greater increase in left insula functional connectivity in the affective network.

Finally, carbamazepine-treated patients displayed poorer accuracy on a sustained attention task at baseline and follow-up compared to healthy volunteers at baseline (63). An increase in sustained attention-related anterior PFC from baseline to follow-up was observed. At follow-up, no significant differences were observed in anterior PFC activity compared to healthy volunteers at baseline.

Antidepressants: Selective Serotonin Reuptake Inhibitors and Serotonin–Noradrenaline Reuptake Inhibitors

For treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs), six manuscripts were identified. Four studies were conducted in mood disorders, with a total of 124 patients scanned before and after treatment. Two studies were conducted in OCD, with a total of 24 patients scanned before and after treatment. Medication type distribution was as follows: 35 escitalopram (26 mood disorders), 31 venlafaxine (26 mood disorders), 27 sertraline (all mood disorders), 22 paroxetine (13 mood disorders), 21 fluoxetine (20 mood disorders), and 12 citalopram (all mood disorders).

Mood Disorders

On an *n*-back task, major depression patients compared to healthy volunteers had slower reaction times at baseline, which did not change after 2 and 8 weeks of SSRI treatment (64). However, compared to healthy volunteers, performance accuracy on the 3-back condition increased over time. Compared to healthy volunteers and over time, no activity changes in the fronto-cingulo-parietal cognitive control network were observed.

Aizenstein and colleagues (65) investigated the effect of SSRI treatment on task performance and brain activity during the preparing to overcome prepotency (spatial incompatibility) task, which assesses cognitive control. Compared to healthy volunteers at baseline, poorer performance accuracy at follow-up was observed in the sample of late-life depression patients treated with paroxetine. From baseline to follow-up, rule applying-related DLPFC, but not response overriding-related ACC, activity increased in patients. At follow-up, DLPFC activity was still lower than healthy volunteers at baseline.

Wagner et al. (66) investigated the effects of SSRI treatment on Stroop task performance and attention and interference-related brain activity. The decrease in response time between baseline and follow-up was greater for incongruent trials than for congruent trials when the SSRI-treated sample was combined with a sample receiving noradrenaline reuptake inhibitors (NRIs; see Noradrenaline Reuptake Inhibitors treatment in Major Depression). From baseline to follow-up, SSRI treatment was associated with widespread decreases in the fronto-cingulo-parietal network during the incongruent condition of the Stroop task (**Table 1**). When SSRI- and NRI-treated patients were combined, no differences in brain activity during the incongruent condition were observed at follow-up, relative to healthy volunteers.

In a large multicenter endeavor, healthy volunteers and remitted depression patients (treated with SSRIs or SNRIs) showed a decrease in response inhibition-related DLPFC activity from baseline to follow-up (67). Relative to healthy volunteers and remitters, non-remitters displayed DLPFC hypoactivity at baseline, which did not increase at follow-up. SSRI remitters and healthy volunteers showed a similar decrease in IPL activity from baseline to follow-up. At baseline, SNRI remitters compared to SSRI remitters and healthy volunteers displayed IPL hypoactivity, which did not increase to the level of healthy volunteers at follow-up.

Obsessive–Compulsive Disorder

Relative to non-responders, SSRI or SNRI treatment responders displayed increased performance accuracy on the *n*-back over time (68). From baseline to follow-up, responders relative to non-responders correspondingly displayed decreased activity in the fronto-cingulo-parietal network during the 1-back and 2-back condition.

Using a task-switching paradigm, Han et al. (69) showed that task-switching costs (task-switching reaction time − task-repeat reaction time) decreased in SSRI-treated patients from baseline to follow-up. However, patients displayed poorer accuracy at baseline and follow-up than healthy volunteers at baseline. From baseline to follow-up, task-switching activity increased in the

fronto-cingulo-parietal network (**Table 1**). Compared to healthy volunteers at baseline, decreased frontal and parietal activity remained and increased insular activity appeared at follow-up (**Table 1**).

Atypical Antipsychotics

For treatment with typical and atypical antipsychotics, seven manuscripts were identified. Two studies were conducted in bipolar disorder, with a total of 21 patients scanned before and after treatment. The remaining five studies were conducted in psychotic disorders, with a total of 60 patients scanned before and after treatment. The 36 patients received risperidone (11 bipolar), 11 ziprasidone (10 bipolar), 13 quetiapine, 3 olanzapine, 2 haloperidol, and 2 aripiprazole. Another 14 patients with psychotic disorder received either risperidone or aripiprazole, but numbers for each treatment were not reported.

Bipolar Disorder

In addition to divalproex (see Anticonvulsant treatment in Bipolar Disorder), Pavuluri and colleagues (62) also investigated the effect of risperidone on response inhibition-related functional connectivity in pediatric mania. From baseline to follow-up and compared to healthy volunteers, a greater increase in insular functional connectivity during response inhibition was observed in an affective functional connectivity network.

Schneider et al. (63) investigated the effect of ziprasidone on sustained attention in pediatric mixed/mania patients. Performance parameters on the continuous performance task (identical pairs version, similar to 1-back task) did not differ among treatment and control groups (over time). From baseline to follow-up and compared to a placebo-treated patient group, the zipradisone-treated group showed a larger increase in right sustained attention-related VLPFC and OFC activity. At days 7 and 28, no significant differences in sustained attention-related brain activity were observed between the entire patient sample (ziprasidone plus placebo) and healthy volunteers at baseline.

Psychotic Disorders

In another study using the preparing to overcome prepotency task, SCZ patients compared to healthy volunteers displayed increased reaction times at baseline and follow-up (70). From baseline to follow-up, response overriding-related ACC activity increased in SCZ patients, whereas rule applying-related DLPFC activity did not. At follow-up, task-induced ACC and DLPFC activity was comparable between SCZ patients and healthy volunteers.

In an open-label quetiapine trial, performance on the *n*-back task did not improve over time (71). However, task-induced left VLPFC and right precuneus activity increased in SCZ patients from baseline to follow-up.

Following treatment with atypical antipsychotics, Keedy et al. (72) reported activity normalization in anterior frontal and parietal areas during a visual attention task (**Table 1**). At follow-up, not all activity had normalized: compared to healthy volunteers, widespread reductions in fronto-cingulo-parietal activity had appeared or remained in SCZ patients (**Table 1**).

In a second study by Keedy et al. (73), patients and healthy volunteers did not differ in performance on the same visual attention task at baseline or follow-up. Activity in supplementary eye fields and parietal cortex normalized from baseline to follow-up (**Table 1**). During a presaccadic task, which probes frontostriatal motor and attention functions, increased left parietal and decreased DLPFC activity was observed from baseline to follow-up.

A final study using atypical antipsychotics in first-episode psychosis reported increased accuracy over time on an attention control task, which was still poorer than healthy volunteers at follow-up (74). In PFC, left SFG and anterior PFC activity increased from baseline to follow-up, although decreases in SFG activity were also reported.

Benzodiazepines

We identified one manuscript using lorazepam plus disulfiram in substance dependence with comorbid anxiety disorder. A total of seven patients were scanned before and after treatment.

Alcohol Use Disorder

On a multisensory Stroop task, alcohol use disorder patients displayed overall slower reaction times than healthy volunteers at baseline (75). While at baseline, alcohol use disorder patients displayed attention and interference-related deactivity in parietal areas, there was slight activity at follow-up (i.e., decreased deactivity) (**Table 1**).

Catechol-*O*-Methyl Transferase Inhibitors

For treatment with catechol-*O*-methyl transferase (COMT) inhibitors, two studies were identified. One study was carried out in smoking dependence; the other was carried out in pathological gambling. The 32 patients were scanned before and after tolcapone treatment.

Smoking Dependence

In a randomized double-blind placebo-controlled crossover design, Ashare et al. (76) observed that performance accuracy on the *n*-back task, relative to placebo, increased after 8 days of treatment with tolcapone. Relative to placebo, patients displayed increased ventromedial PFC (VMPFC) deactivity. On tolcapone relative to placebo, Val/Val carriers of the COMT gene displayed decreased medial PFC (MPFC) activity and increased (i.e., more) VMPFC deactivity during the task, while Val/Met carriers displayed increased VMPFC and right DLPFC activity.

Pathological Gambling

Pathological gambling patients and healthy volunteers showed similar overall accuracy on a Tower of London planning task (77). From baseline to follow-up, planning-related fronto-cingulo-parietal activity increased and seemingly normalized to that of healthy volunteers at baseline (**Table 1**).

Nicotinic Receptor Agonists

We identified three papers (two unique samples) using nicotinic receptor agonists, with a total of 38 patients scanned before and after treatment. One study used α4β2 nicotinic receptor agonist varenicline in 22 smoking-dependent individuals. Another study used 3-(2,4-dimethoxybenzylidene)-anabaseine (DMXB-A),

a partial α7 nicotinic agonist, as an adjunctive treatment in 16 non-smoking SCZ patients on stable antipsychotic treatment.

Smoking Dependence

Response times for correct trials on the *n*-back decreased on varenicline relative to placebo in highly dependent abstinent smokers, but not in their lowly dependent counterparts (78). Moreover, on varenicline relative to placebo, MPFC and DLPFC activity increased, specifically on the 2-back and 3-back level. In addition, whole brain analyses revealed frontal cortex activity decreases on varenicline relative to placebo, with peak deactivations detected in the right SFG and left IFG.

Psychotic Disorders

Relative to placebo, no changes in the fronto-cingulo-parietal network were observed during a visual attention task after a 1-month treatment with 75 and 150 mg of DMXB-A (79). However, differences in frontal and parietal default mode network activity were observed between the placebo and DMXB-A session (**Table 1**) (80).

Noradrenaline Reuptake Inhibitors

For treatment with NRIs, five studies were identified. Three studies were conducted in ADHD (two pediatric and one adult sample), one in major depression, and one in SCZ (adjunctive treatment). A total of 64 patients were scanned before and after treatment, of which 56 received atomoxetine and 8 received reboxetine (all major depression).

Attention-Deficit/Hyperactivity Disorder

Similar to MPH-treated patients, accuracy increased on No-Go trials from baseline to follow-up in those receiving atomoxetine (81). Moreover, reaction times and reaction time variability decreased. From baseline to follow-up and similar to the MPH-treated group, primary motor cortex activity decreased during the response inhibition task. MPH and atomoxetine seemed to produce differential effects on the fronto-cingulo-parietal cognitive control network (**Table 1**): atomoxetine increased and MPH decreased activity from baseline to follow-up.

Bush et al. (82) reported that performance on an attention control task did not change over time or relative to placebo-treated patients. From baseline to follow-up, frontal cortical and parietal activity (**Table 1**) during an interference task increased in an atomoxetine-treated cohort of patients.

Similar to MPH-treated patients, reaction times on a Stroop task decreased over time in atomoxetine-reated patients (83). At brain level, differential effects of MPH and atomoxetine were observed. From baseline to follow-up and relative to MPH, greater increases in left DLPFC and ACC activity and a smaller increase in left IFG activity were reported.

Major Depression

In addition to SSRIs (see Antidepressant treatment in Mood Disorders), Wagner et al. (66) also investigated the effects of NRIs on response interference-related brain activity. Whereas SSRIs decreased fronto-cingulo-parietal network activity (**Table 1**), reboxetine did not.

Psychotic Disorders

Friedman et al. (84) investigated the effect of adjunctive atomoxetine pharmacotherapy on *n*-back-related brain activity in SCZ patients on stable treatment with atypical antipsychotics. Performance parameter changes were not observed among groups or over time. At follow-up relative to placebo-treated patients, increases in left DLPFC activity were observed.

Noradrenergic Receptor Agonists

We identified one paper using $\alpha 2_A$ noradrenergic receptor agonist guanfacine, investigating 12 pediatric ADHD patients before and after treatment.

Attention-Deficit/Hyperactivity Disorder

From baseline to follow-up and compared to placebo-treated patients, 6- to 8-week treatment with guanfacine was not associated with improved accuracy, reaction times, or response inhibition-related brain activity in the fronto-cingulo-parietal network (85).

DISCUSSION

The aim of this systematic review was to summarize the impact of pharmacological interventions for psychiatric disorders on the fronto-cingulo-parietal cognitive control network and to relate this to plausible neurochemical mechanisms of action. Here, we will first discuss the evidence per treatment class, followed by a review of transdiagnostic commonalities as potential markers for future procognitive treatments.

Pharmacological Interventions, Their Effects on Functional Brain Correlates of Executive Functions and Neuropharmacological Mechanism

Cholinergic Targets

Despite the pivotal role of acetylcholine in executive functions (86, 87), few potentially procognitive cholinergic agents are currently available, with actylcholinesterase inhibitors and nicotinic receptor agonists used most frequently.

Acetylcholinesterase Inhibitors

With a placebo-controlled and placebo-controlled crossover design, the available preliminary evidence for adjunctive acetylcholinesterase inhibitors in SCZ was of good quality. In line with a large number of placebo-controlled clinical trials (88–92), adjunctive rivastigmine or donepezil treatment did not improve performance on attention and working memory tasks in SCZ. Moreover, in contrast to studies in Alzheimer's disease (93, 94), two out of three manuscripts did not report task-related increases in fronto-cingulo-parietal activity (59, 60). Only Nahas et al. (58) observed increased IFG activity during a verbal fluency task after 12 weeks of treatment, a region also previously associated with verbal fluency (95) and likely associated with the Go/No-Go behavior required for this task. Kumari et al. (60) observed increased left SFG activity in placebo-treated patients over time, but not in the rivastigmine-treated patient group. These

between-study differences may be explained by sample size (6 vs. 11 participants) or task demands, with verbal fluency tasks being dependent on lexical access speed and vocabulary size (96), in addition to attention and working memory.

There was, however, evidence for increases in occipital cortex and cerebellum activity (58, 59), previously reported to be related to visual attention, stimulus encoding, or motor speed (97, 98). Indeed, meta-analytic evidence suggests that acetylcholinesterase inhibitors may increase motor speed in SCZ (99), possibly explaining increased cerebellar activity.

The absence of any marked and consistent effects of acetylcholinesterase inhibitors on the fronto-cingulo-parietal cognitive control network in SCZ may be related to the suspected abnormalities in the cholinergic system. In SCZ, abnormalities have been observed at the receptor level, with evidence for a decrease in α7 nicotonic (100), β2 (101), and muscarinic receptors (102). Acetylcholinesterase inhibition, compared to direct targeting of receptors, may therefore not be the most efficient way to improve executive functions in SCZ. Second, tobacco desensitizes α7 and α4β2 nicotonic receptors (103, 104) and many participants in the available studies smoked tobacco. This could further decrease the procognitive potential of acetylcholinesterase inhibitors, although upregulated β2 receptors in smoking SCZ have also been associated with improved executive functions (105), requiring further investigation. Finally, all participants were already on atypical antipsychotics, which have been shown to increase frontal cortex acetylcholine release (106), fronto-cingulo-parietal activity (107, 108), and modestly improve performance on neuropsychological tests (36) (also see Atypical Antipsychotics), perhaps indicating a ceiling effect.

Thus, the current preliminary evidence suggests that adjunctive acetylcholinesterase inhibitors in SCZ do not markedly impact the fronto-cingulo-parietal cognitive control network, but may increase occipital cortex and cerebellum activity. Given the quality of the available evidence, these results likely reflect treatment effects, rather than practice or iatrogenic effects. In order to determine if the cholinergic system can be targeted to increase executive functions in SCZ, selective and direct targeting of nicotinic and muscarinic receptors may be a more fruitful strategy, although lack of specificity for the receptor subtypes has hampered the development of suitable drugs.

Nicotinic Receptor Agonists

The only available study for acetylcholine nicotinic receptor agonists in smoking dependence was a placebo-controlled crossover design, which reported decreased *n*-back reaction times in highly dependent smokers while on varenicline. Moreover, on varenicline relative to placebo, DLPFC and ACC activity increased in the entire sample of smoking-dependent individuals, while activity in other frontal cortical areas decreased. Modulation of these areas is in line with recent meta-analytic evidence and likely reflects varenicline's ability to optimize activity of the cognitive control network while suppressing task-irrelevant activity of the default mode network (109). Behaviorally, these observations are in agreement with repeated dosing evidence showing that varenicline improves several aspects of executive functions in smokers (110–112) and non-smokers (113). Varencline's ability to modulate fronto-cingulo-parietal activity is promising and eagerly awaits replication in other psychiatric disorders.

In non-smoking SCZ patients, partial α7 agonist DMXB-A was not associated with activity changes in the fronto-cingulo-parietal network during a visual attention task. However, task-related changes in hippocampal activity (79) and suppression of default mode network activity in frontal cortical and parietal areas (80) were observed. While no other data for SCZ were available, the trial evidence for DMXB-A (114, 115) and varenicline (116–120) in psychotic disorders has been mixed, perhaps related to underlying cholinergic abnormalities or smoking status. Here, the use of fMRI and neuropsychological tasks that emphasize working memory, response inhibition, and action selection abilities could be useful in assessing DMXB-A's potential procognitive abilities in SCZ.

Varenicline is a nicotinic receptor partial agonist at α4β2 receptors and full agonist at α7 receptors, and DMXB-A is a partial agonist at α7 receptors. Both β2- and α7-selective compounds increase frontal cortex dopamine release in the rat (121), offering an explanation for varenicline and DMXB-A's putative activity-modulating abilities in frontal cortical areas. Neuropharmacologically, α7 and α4β2 in frontal cortex (121), α4β2 receptors expressed on ventral tegmental area neurons (122) and α7 receptors expressed on glutamatergic projections to the ventral tegmental area (123) seem to underlie the increase in dopamine release.

Anticonvulsants

While anticonvulsants were originally developed to treat epileptic seizures, the majority of them have been shown to exert mood-stabilizing effects in bipolar (124, 125). Given that modulation of glutamatergic and γ-aminobutyric acid (GABA) activity is a common mechanism of these agents, and that excessive PFC glutamatergic signaling may contribute to cognitive impairments (126), it seems plausible to suggest that they could modulate executive functions.

With two open-label trials and one placebo-controlled study, the evidence for anticonvulsants in bipolar disorder was of moderate quality. In the open-label trials, there was no evidence for improvements in task performance (61, 63). This is in contrast to the only available placebo-controlled study, where divalproex treatment seemingly normalized response inhibition, but only when combined with a parallel group of risperidone-treated bipolar patients (62).

In the open-label trials, widespread normalization (increases) of anterior PFC and MPFC hypoactivity was observed after anticonvulsant treatment (61, 63). However, practice and placebo effects could not be excluded because of the lack of a placebo-controlled group and absence of prospective data for healthy volunteers (**Table 1**). In line with the findings of increased PFC activity in the open-label studies, subgenual ACC and insular functional connectivity increased during a Go/No-Go task in the placebo-controlled study (62). The regional specificity of these findings is noteworthy, given the consistent involvement of the ACC and insula in conflict monitoring and response inhibition (30). This may point toward treatment effects, but it is important that the findings for carbamazepine and lamotrigine are now replicated in placebo-controlled studies.

The inhibitory actions of lamotrigine, carbamazepine, and sodium valproate (127–130) at ion channels and *N*-methyl-D-aspartate (NMDA) receptors (131) are essential in modulating extracellular glutamate and GABA concentrations. Magnetic resonance spectroscopy studies in bipolar disorder have revealed alterations in frontal cortex, particularly ACC, glutamate, and glutamine concentrations (132, 133). Moreover, treatment with anticonvulsants (132), notably divalproex (134), alters VLPFC and ACC glutamate and glutamine levels, reflecting changes in glutamate concentrations, GABA concentrations, or both.

Summarizing, there is preliminary evidence that anticonvulsants impact, specifically increase, fronto-cingulo-parietal, especially ACC, activity in bipolar disorder, possibly reflecting changes in glutamate and/or GABA release at the neuronal level, and increased response inhibition at the behavioral level.

Antidepressants

Although impressive in total sample size, the quality of evidence for antidepressants in depression and OCD was suboptimal, with five out of six studies employing an open-label design. Moreover, four out of six studies only had access to healthy control data at baseline or did not utilize a control group (**Table 1**). This complicates interpretation of the findings and increases susceptibility to practice, placebo and, more generally, iatrogenic effects.

With the exception of one study reporting a greater increase in 3-back performance over time in patients vs. healthy volunteers (64), there was no evidence for improved task performance following antidepressant treatment in depression. These results are generally in line with clinical trials showing no marked effects of antidepressants on cognitive control in depression (135), a domain that all available studies in depression assessed. Nonetheless, they are puzzling, given the presence of response inhibition deficits in depression (136), the proposed role of serotonin in inhibitory control (40), and the observation that serotonergic manipulations modulate the cognitive control network in healthy volunteers (137–139).

Two studies in depression reported activity decreases over time, observing normalized DLPFC activity during a response inhibition task (67) and normalized frontal cortical and parietal activity during an interference/conflict resolution task (66) following antidepressant treatment. Moreover, there was an overall greater engagement of frontoparietal regions with increasing *n*-back difficulty in patients vs. healthy volunteers (64), consistent with the observation of DLPFC hyperactivity during the *n*-back task in untreated depression (140). Taken together, these data suggest that SSRIs decrease frontal cortical and parietal hyperactivity in treatment responders, in spite of any marked performance changes.

A modest increase in DLPFC activity was observed during a cognitive control task, which at follow-up was still lower than healthy volunteers at baseline (65). The reported increase in DLPFC activity could have been attenuated by practice effects, given that steady declines in task-related activity have been reported over time in healthy volunteers (64, 67) and the fact that this study only had access to healthy volunteer data at baseline. Moreover, the seemingly contrasting observations of increased and decreased PFC activity may also be related to diagnosis: DLPFC activity increases were observed in late-life depression, while studies reporting anterior PFC decreases were conducted in major depression (**Table 1**). A final explanation could be the significant variation in treatment duration, ranging from 6 to 12 weeks, which is especially noteworthy in light of the delayed actions of SSRIs (141, 142).

Serotonin–noradrenaline reuptake inhibitor treatment in depression did not seem to impact fronto-cingulo-parietal activity (67). This is in line with the only available study in depression directly comparing serotonergic and noradrenergic agents (66), where SSRIs were associated with decreased parahippocampal and amygdalar activity, and reboxetine with slightly increased activity in these regions (NRIs in other disorders discussed in Section "Noradrenaline Reuptake Inhibitors"). The differential effect of SSRIs, SNRIs, and NRIs on attention and cognition-related brain function may be related to regional variation in serotonin transporter (143), noradrenaline transporter (144), and serotonin receptor subtype 1_A (5HT1A) (145) expression. Still, they are surprising in light of the well-established modulating effects of NRIs on fronto-cingulo-parietal, specifically IFG, activity in ADHD (81, 83), and healthy volunteers (146).

All in all, the available results in depression suggest an effect of serotonergic treatment on the fronto-cingulo-parietal cognitive control network, but interpretation is severely hampered by a lack of randomized double-blind trials. In the absence of clear performance changes, we speculate that these activity changes could reflect improvement in the affective domain. Indeed, fronto-cingulo-parietal activity (changes) correlated with Hamilton Rating Scale for Depression scores (64, 66), and ACC metabolism predicts treatment response in depression (147).

The preliminary results in OCD were mixed on the level of performance and activity (changes), which could be related to study design (open label vs. double blind) or reference group (treatment responder vs. healthy volunteers at baseline) (68, 69). There were some indications of performance improvements, such as increased accuracy, in SSRI/SNRI treatment responders (68) and decreased reaction times from baseline to follow-up (69). However, comparison with a control group over multiple time points is essential to disentangle practice effects from treatment effects.

Atypical Antipsychotics

The quality of the evidence for atypical antipsychotics was moderate: three out of seven studies employed a randomized double-blind design, and six out of seven studies had baseline and follow-up data of a control group (**Table 1**).

Especially in psychotic disorders, atypical antipsychotics have been associated with modest improvements in executive function domains such as response inhibition, planning, and immediate recall (36, 148, 149). One out of two included studies in bipolar disorder reported increased task performance, with risperidone-treated patients showing comparable response inhibition to healthy volunteers but only when combined with a divalproex-treated group (also see Anticonvulsants) (62). In psychotic disorder, only performance on a visual attention task normalised (73) and two studies reported no performance differences at baseline and follow-up, relative to healthy volunteers (71, 72). Thus, there

seems to be some overlap with clinical trials in terms of modestly improved executive functions on atypical antipsychotics.

Regardless of psychiatric disorder, the most consistent observation was increased, often normalized, anterior PFC (63, 70, 71) ACC (70), and parietal (73) activity following atypical antipsychotics treatment, the great majority being risperidone. Increased fronto-cingulo-parietal activity has also been observed when SCZ patients were switched from typical to atypical antipsychotics (107, 108) and from 4 to 8 weeks of treatment with olanzapine (150), all in all showing a consistent picture of increased fronto-cingulo-parietal activity on atypical antipsychotics. Outside of the fronto-cingulo-parietal network, decreases in ventral (74) and dorsal (72) striatal activity were observed in psychotic disorder. A correlation between caudate activity and risperidone dose (73) was also reported, consistent with the notion that antipsychotics decrease striatal dopaminergic hyperactivity.

Atypical antipsychotics are thought to increase frontal cortex DA release *via* $5HT1_A$ agonism (106, 151–153) and $5HT2_A$ antagonism (154, 155). In addition, increased frontal cortex acetylcholine and serotonin release has also been observed following administration of atypical antipsychotics (106, 151, 154). The observed increases in fronto-cingulo-parietal activity following atypical antipsychotics treatment may therefore be underlain by increased dopaminergic, serotonergic, and/or cholinergic activity in frontal cortex and their downstream effects. While the behavioral, neuroimaging, and neuropharmacological evidence seems to point toward modest procognitive effects of atypical antipsychotics, especially psychotic disorders are in need of replication with double-blind randomized designs to understand the exact extent of normalization within the fronto-cingulo-parietal network.

Benzodiazepines

With only one open-label study identified, the results for benzodiazepines were preliminary. There was no evidence for improved performance, and some hints at decreased parietal hyperactivity and decreased temporal hypoactivity at follow-up, although these activity changes might partly reflect practice effects.

Catechol-*O*-Methyl Transferase Inhibitors

A placebo-controlled crossover and open-label study were identified for COMT inhibitors, suggesting moderate quality of the available preliminary evidence.

One out of two studies reported performance changes; in smoking dependence, *n*-back performance accuracy increased on tolcapone, and there was an effect of COMT genotype on reaction times (76) (**Table 1**). Task-related activity changes were observed in both smoking dependence and pathological gambling, with the former showing increased VMPFC deactivity on tolcapone (76) and the latter normalized fronto-cingulo-parietal hypoactivity, albeit to activity of healthy volunteers at baseline and in the absence of a placebo-controlled group (77). These results are in line with tolcapone's effect in healthy volunteers, where it has been reported to increase *n*-back performance (156) and optimize task-related brain activity (156, 157).

Although preliminary and modest in nature, the results for COMT are favorable and could suggest potential procognitive effects that remain to be replicated in large placebo-controlled clinical trials. Interestingly, tolcapone does not affect extracellular catecholamine concentrations when administered alone, but increases striatal and frontal cortex dopamine release after L-DOPA (158, 159) and clozapine (160) administration. This may suggest that the catecholamine-increasing effect of tolcapone on the fronto-cingulo-parietal network could be even greater in medicated individuals with Parkinson's disease or psychotic disorder, opening up new avenues for adjunctive treatment.

Noradrenaline Reuptake Inhibitors

With three randomized studies (one reported to be double-blind), all having included a MPH-treated patient group and one additional placebo-treated patient group (**Table 1**), the evidence for atomoxetine in ADHD was of moderate to good quality. In line with clinical trial evidence (35), increased performance on response inhibition tasks was observed following atomoxetine treatment (81, 83).

Meta-analytical evidence in ADHD suggests that MPH among others consistently impacts IFG, dorsal ACC, and SMA activity (30), which were all areas consistently modulated by atomoxetine treatment (**Table 1**) and involved in conflict monitoring, response inhibition, and action selection (40). There were, however, differences between the two agents, such that atomoxetine and MPH exerted opposing effects on the same regions (81, 82) or that atomoxetine modulated task-relevant activity in one part of the fronto-cingulo-parietal network (e.g., ACC and DLPFC activity), while MPHs actions affected another part of the network (e.g., IFG) (83).

These results suggest that atomoxetine and MPH impact common substrates of the fronto-cingulo-parietal network, but also have a certain local and global task-dependent uniqueness. One tentative explanation could be that atomoxetine and MPH have almost comparable procognitive effects *via* differing underlying neurochemical mechanisms. MPH and atomoxetine's dopamine- and noradrenaline-increasing properties (161) are for a major part directed to D1 and $\alpha 2_A$ adrenergic receptors, the former involved in suppressing noise (162) and the latter in enhancing signal (163) of neuronal networks. Moreover, the atomoxetine-induced increase in noradrenaline levels in frontal cortex decreases after prolonged exposure, while this is not the case for MPH (164). The neuropharmacological properties of MPH and atomoxetine may differentially affect the reorganization of functional brain networks.

In contrast to amphetamine (165) and in line with previous work (166), adjunctive atomoxetine treatment in antipsychotics-treated SCZ patients did not improve task performance. Despite any performance changes, task-related activity increases in DLPFC were observed, as well as an increase in posterior cingulate gyrus activity. These are regions typically modulated by atomoxetine in ADHD (81). While preliminary, the combination of atypical antipsychotics and atomoxetine may have led to overstimulation of frontal cortex dopamine and noradrenaline release, thereby missing the narrow window in which frontal cortex dopamine and noradrenaline levels optimally mediate cognitive performance (163, 167). Replication with SCZ patients on typical antipsychotics or MPH as an adjunctive treatment may shed further light on these findings.

Noradrenergic Receptor Agonists

While there were no main effects of $\alpha 2_A$ noradrenergic agonist guanfacine on response inhibition or associated brain function, this agent is clinically efficacious in treating symptoms of ADHD (168). Moreover, in smoking dependence, guanfacine modulates response inhibition and conflict resolution-related activity in among others SMA, DLPFC, VMPFC, and insula (169). In comparison to MPH and atomoxetine, guanfacine's actions are confined to $\alpha 2_A$ noradrenergic receptors, thereby specifically enhancing signal in working memory networks (163). Direct comparison of guanfacine with atomoxetine and MPH could be valuable in elucidating the degree to which the latter two compounds modulate fronto-cingulo-parietal activity *via* a signal-increasing mechanism.

Common Transdiagnostic Changes in the Fronto-Cingulo-Parietal Network as Indicators of Successful Treatment

While executive function deficits are a universal symptom of psychiatric disorders, the underlying causes are not known. What is clear is that executive functions are underlain by an intricate and widely distributed network of brain regions. Theoretically, alterations in any of these regions can negatively affect network integrity, thereby giving rise to executive function deficits. As a result, pharmacological treatment of executive function deficits remains complex, reflected in the unsatisfactory treatment across psychiatric disorders. We identified common transdiagnostic changes in fronto-cingulo-parietal activity, which could serve as treatment markers.

Despite differences in experimental designs, treatment duration, and dosage, there were notable transdiagnostic effects of pharmacological agents on the fronto-cingulo-parietal network. In studies that also showed beneficial behavioral effects, or for which clinical trial data suggested beneficial effects, common activity changes in the fronto-cingulo-parietal network were (I) enhancement of activity in task-relevant areas and (II) suppression of activity in task-irrelevant areas.

In smoking dependence, tolcapone further suppressed activity in task-irrelevant areas such as the VMPFC (76), while in pathological gambling, it increased task-relevant fronto-cingulo-parietal activity (77). In line with the agent's neuropharmacological action, the exact nature of activity changes was dependent on COMT genotype (**Table 1**). Similarly, nicotinic receptor agonist varenicline increased DLPFC and ACC activity in smoking dependence (78) and suppressed parietal and frontal cortical default mode network activity in SCZ (80). Atomoxetine, in most cases, increased task-relevant activity in DLPFC, ACC, IFG, and IPL in ADHD (81–83). Lastly, atypical antipsychotics increased DLPFC, ACC, and parietal cortex activity (70, 73), and decreased VMPFC activity (72). Overall, these results suggest positive predictive value of increased task-related fronto-cingulo-parietal activity as a marker of successful pharmacological treatment.

These were also transdiagnostic commonalities that displayed a degree of negative predictive value. Notably, increased task-relevant DLPFC activity was observed after adjunctive atomoxetine treatment in SCZ, together with increased task-irrelevant posterior cingulate activity, a region thought to be associated with the default mode network (80). Moreover, in depression, non-remitters showed task-relevant DLPFC hypoactivity (67). Finally, acetylcholinesterase inhibitors in SCZ did not consistently modulate fronto-cingulo-parietal network activity (58–60).

A final common observation was that the effects of pharmacological agents on the fronto-cingulo-parietal network were often lateralized. Unilateral effects could be related to lateralization of frontoparietal networks at rest (170). Indeed, changes in unilateral frontoparietal networks have also been observed following dopaminergic challenges (171). Lateralized functional networks could be the result of lateralized projections at the cellular level, which has been shown for among others dopamine (172), serotonin (173), and glutamate (174). Assessing laterality of the observed activity changes could be helpful in determining the specificity of treatment effects.

Conclusion and Future Directions

The available evidence suggests that dopamine, noradrenaline, and acetylcholine agonists are most consistently associated with activity changes in the fronto-cingulo-parietal network, as measured with fMRI. Across disorders, increased activity in task-relevant areas or decreased activity in task-irrelevant areas were the most consistent findings, demonstrated by good positive and moderate negative predictive value. However, in order to fully assess the potential of these markers, more randomized double-blind studies are necessary.

The current review highlights the potential of a dimensional, transdiagnostic approach in future (pharmacological) neuroimaging studies, thereby paralleling a shift that is currently taking place in the field of clinical diagnostics and management. The search for procognitive agents has thus far been carried out within the context of categorical classifications, which has not lead to any major breakthroughs in the development of treatments.

A surprising observation was the lack of selective cholinergic, especially muscarinic, and glutamatergic, notably NMDA receptor, agents. Preclinical and proof-of-concept trial evidence have demonstrated promising procognitive potential for M1 allosteric modulators (86, 175) and selective NMDA antagonists (176). The lack of clinical trial and neuroimaging evidence may reflect unavailability of such compounds or potential safety issues of the available compounds (177). A recent initiative that may facilitate testing of novel compounds is the Medicine Chest initiative by the ECNP (www.ecnp.eu), which could aid clinical researchers in gaining access to new pharmacological tools.

AUTHOR CONTRIBUTIONS

DH and TA performed literature search, writing, and interpretation of the data.

FUNDING

DH was supported by a Kootstra post-doctoral Fellowship. TA was supported by an NWO VIDI.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

PERSPECTIVE
published: 27 June 2016
doi: 10.3389/fpsyt.2016.00117

Mindfulness-Based Cognitive Therapy and the Adult ADHD Brain: A Neuropsychotherapeutic Perspective

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Attention-deficit/hyperactivity disorder (ADHD) is a recognized serious mental disorder that often persists into adulthood. The symptoms and impairments associated with ADHD often cause significant mental suffering in affected individuals. ADHD has been associated with abnormal neuronal activity in various neuronal circuits, such as the dorsofrontostriatal, orbitofrontostriatal, and frontocerebellar circuits. Psychopharmacological treatment with methylphenidate hydrochloride is recommended as the first-line treatment for ADHD. It is assumed that medication ameliorates ADHD symptoms by improving the functioning of the brain areas affected in the condition. However, side effects, contraindications, or non-response can limit the effectiveness of a psychopharmacological treatment for ADHD. It is therefore necessary to develop non-pharmacological interventions that target neuronal mechanisms associated with the condition in the same way as pharmacological treatment. We think that mindfulness meditation employed as a neuropsychotherapeutic intervention could help patients with ADHD to regulate impaired brain functioning and thereby reduce ADHD symptoms. In this paper, we highlight the mechanisms of such mindfulness meditation, and thus provide a rationale for further research and treatment development from a neuropsychotherapeutic perspective. We conclude that mindfulness meditation employed as a neuropsychotherapeutic intervention in therapy is a promising treatment approach in ADHD.

Keywords: neuropsychotherapy, ADHD, adult, MBCT, non-psychopharmacological treatment

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Gianluca Serafini, University of Genoa, Italy
Philipp Ernst Eich, Psychiatrie Baselland, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *09 March 2016*
Accepted: *14 June 2016*
Published: *27 June 2016*

Citation:
Bachmann K, Lam AP and Philipsen A (2016) Mindfulness-Based Cognitive Therapy and the Adult ADHD Brain: A Neuropsychotherapeutic Perspective. Front. Psychiatry 7:117. doi: 10.3389/fpsyt.2016.00117

CURRENT STATE OF TREATMENT OF ADHD IN ADULTHOOD

Attention deficit/hyperactivity disorder (ADHD) is a serious mental disorder characterized by three core symptoms: inattention, impulsivity, and hyperactivity. In up to 60% of cases, ADHD symptoms persist into adulthood (1). It has been estimated that about 3.4% of the adult population is affected by ADHD (2). The clinical picture of the condition is quite heterogeneous with respect to the expression and severity of symptoms, as well as its pathogenesis (3, 4).

It is assumed that the disorder relies strongly on impairments to neurobiological function (5, 6). Individuals with ADHD show abnormal neuronal activity in dorsofrontostriatal, orbitofrontostriatal, and frontocerebellar circuits (6). Furthermore, abnormal functional connectivity in the default-mode network (DMN) has been suggested (7).

Adults with ADHD often suffer from comorbid disorders (e.g., depression or anxiety disorders) and negative psychosocial consequences (8). Therefore, a multimodal treatment approach that takes

into consideration both the ADHD and the comorbid disorders and psychosocial functioning is currently the gold standard in the treatment of adult ADHD (9).

Psychopharmacological treatment with methylphenidate hydrochloride is recommended as the first-line treatment for ADHD core symptoms (9). Methylphenidate influences dopaminergic and noradrenergic systems of the striatum, prefrontal cortex, locus coeruleus, and somatosensory cortex. Dopamine plays an important role in drive and motivation, and noradrenalin in attentional processes (10–12). Therefore, it has been suggested that the positive effects of methylphenidate on ADHD can be attributed to improving the functioning of brain areas involved in attentional and motivational processes (13). These positive effects can be augmented when combined with individual or group cognitive behavioral therapy (14).

However, while psychopharmacological treatment with methylphenidate has undoubted positive effects on ADHD symptoms, it also has significant limitations. About 20–50% of adult ADHD patients are non-responders (15). Also, a study by Tucha et al. (16) showed that although methylphenidate reduced deficits in attentional processes, it did not achieve normalization. Furthermore, contraindications such as hyperthyroidism, pregnancy, hypertonia, or substance abuse can prohibit treatment with methylphenidate (9, 17, 18). For instance, in a study investigating the efficacy of a combination of cognitive behavioral group psychotherapy, individual clinical management, and methylphenidate in a clinical sample, contraindications in about 20% of participants meant that they could not be treated with methylphenidate (14). Even if treatment with methylphenidate is possible, adverse side effects can occur. These most frequently include headaches, loss of appetite and weight, insomnia, internal unrest, and increased blood pressure and pulse (10). As a result, some patients prefer non-medical treatment.

Given the limitations of treatment with methylphenidate, it is worth considering alternative treatment approaches that target both the underlying neurobiological mechanisms and the psychosocial difficulties of patients with ADHD. From our point of view, this is best achieved by administering treatment from a neuropsychotherapeutic perspective. Such an approach incorporates neurobehavioral interventions to enhance the functioning of brain regions affected in ADHD and specific cognitive behavioral interventions. In mindfulness-based cognitive therapy (MBCT), conventional cognitive behavioral interventions are combined with mindfulness meditation, which can be understood as a form of mental training (19). Mindfulness signifies an open and alert state of mind. The person's attention stays in the present moment, and sensations such as thoughts and feelings that arise are perceived and observed non-judgmentally (20). There is preliminary evidence that mindfulness meditation can improve the functioning of brain mechanisms underlying neuropsychological capacities impaired in ADHD, such as attention control and emotion regulation (19). We think that mindfulness meditation in patients with ADHD could help them to regulate brain functioning and thereby ameliorate their symptoms.

This paper aims to illustrate our concept of a neuropsychotherapeutic approach for ADHD in adulthood.

A search for trials on treatment, mindfulness, neuropsychotherapy, and psychotherapy in adult ADHD was conducted in the following bibliographic databases: PubMed, Embase, Medline, and Central (The Cochrane Central Register of Controlled Trials). The following terms were used: (ADHD OR (attention deficit) OR (attention deficit) OR hyperactivity*) AND (non-psychopharmacological treatment OR treatment OR therapy OR mindfulness OR psychotherapy OR neuropsychotherapy OR neuropsychology) AND (adult). Studies were selected and included according to their relevance for the subject.

WHAT IS NEUROPSYCHOTHERAPY?

The concept of neuropsychotherapy represents the link between neuropsychology and psychotherapy. A neuropsychotherapeutic approach brings a neuroscientific perspective to therapeutic issues and aims to target underlying brain mechanisms that could be an obstacle to recovery in traditional therapy (21, 22).

We define "neuropsychotherapy" as an approach that integrates cognitive behavioral therapy with neurobehavioral treatment. Neurobehavioral treatment refers to behavioral interventions that deliberately target neuronal mechanisms associated with psychiatric disorders, in the same way as pharmacological or surgical treatments (22).

Since neuropsychotherapy targets neurobiological mechanisms, as well as observable symptoms or cognitive, behavioral manifestations of underlying neurobiological mechanisms, multiple therapeutic interventions are used. As in conventional psychotherapy, cognitive and behavioral interventions are employed for psychoeducative purposes and to bring about change in problematic cognitive and behavioral patterns. In addition, neuropsychological interventions are used. That is, affected neuronal structures are identified through neuropsychological assessment and neuroimaging. Subsequently, neurobehavioral interventions are employed to strengthen the functioning of those neuronal structures *via* concrete, intensive, and repetitive stimulation (21).

There is evidence that intensive and repetitive targeting of dysfunctional neuronal structures can ameliorate psychiatric disorders and improve brain functioning. In one study, patients with severe unipolar depression received neurobehavioral "cognitive control training" for 2 weeks, aimed at activating the prefrontal cortex, which it has been suggested plays an important role in depressive symptoms such as rumination. They were compared to a control group who received treatment as usual. Participants in the intervention group displayed a significantly greater decrease in depressive symptoms and rumination than participants in the control group. In addition, participants who received the cognitive control training showed normalization of brain functions targeted by the intervention (22).

Furthermore, it has been proposed that the success of cognitive behavioral therapy in treating anxiety disorders may be attributable to the modification of underlying, dysfunctional neuronal systems, as a result of the concrete, intense, and repetitive stimulation induced by exposure sessions (21). For instance, neuroimaging studies in OCD (obsessive compulsive disorder) samples (23, 24) revealed that exposure is associated with improved activity in brain areas involved in obsessive compulsive behavior.

It is recognized that, owing to neuronal plasticity, altered brain functioning can be modified by intense, prolonged, and regular therapeutic interventions (21, 22, 25), leading to improved psychological functioning. Therefore, the neuroscientifically informed implementation of neurobehavioral interventions in conventional psychotherapy appears to be a promising approach to improving treatment outcomes (22). It would appear particularly promising for treatment of a condition such as ADHD, which is known to be significantly related to structural, functional, and neurochemical brain abnormalities (26).

WHY NEUROPSYCHOTHERAPY IN ADHD?

There is growing evidence that ADHD psychopathology is closely related to dysfunctions in multiple neuronal systems implicated in higher-level cognitive functions, as well as sensorimotor processes and the DMN (a brain network that is active in the resting state and inactive during task performance), which causes impairments in executive functioning (26), including in attentional processes such as sustained attention and set-shifting, impulse control, and working memory. ADHD symptoms are thought to reflect altered connectivity within and among several neural networks, rather than abnormal functioning of discrete, isolated brain regions (5). It has been suggested that mostly prefrontal–striatal–cerebellar circuits are impaired in ADHD in adulthood, specifically the prefrontal cortex, basal ganglia, and cerebellum are associated with ADHD (27, 28). The first of these neural circuits are frontostriatal loops, involved in response output control/response suppression, working memory, and response selection. Impairments are also found in frontocerebellar loops, responsible for the temporal information processing needed in timing and alerting the brain to new information. Finally, frontolimbic loops involved in avoidance conditioning and reinforcement learning are relevant to ADHD (27) (see **Figure 1**).

Frontoparietal Network

A meta-analysis of neuroimaging studies of ADHD in adulthood revealed ADHD-related hypoactivation located in the frontoparietal network, which includes the lateral frontal pole, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), anterior PFC (aPFC), lateral cerebellum, anterior insula, and the caudate and inferior parietal lobe (5, 29). The frontoparietal network is known as the executive control circuit (30). It guides decision making by integrating external information with internal representations (5). It provides the flexibility to configure information processing when task demands change, and is involved in goal-directed executive processes (31). Hypoactivation in the frontoparietal network is consistent with executive dysfunction in ADHD in adulthood (26).

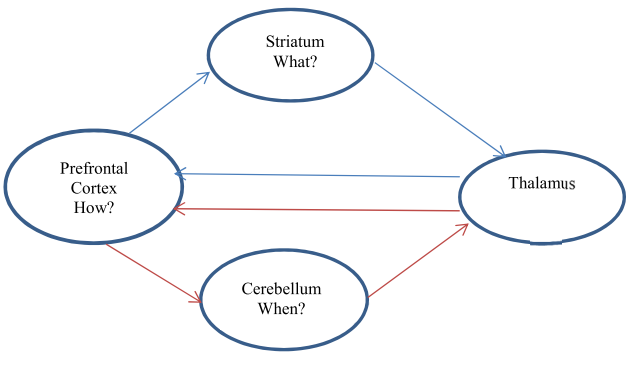

FIGURE 1 | Cerebellar pathways affected in ADHD.

Attentional Network

The functioning of the dorsal and ventral attentional networks, which are central parts of the attentional regulatory system, also seems to be impaired in ADHD (5, 32). The ventral attentional network includes the temporoparietal junction, the supramarginal gyrus, frontal operculum, and anterior insula (32). It is involved in attentional reorienting to relevant external stimuli and in interrupting ongoing activity when necessary. To prevent shifts of attention to irrelevant objects, suppression of this network is needed (33). It has been suggested that hyperactivation of the ventral attentional network may explain distractibility, which is a main symptom of ADHD (26). The dorsal attentional network, which is anchored by the intraparietal sulcus and the frontal eye fields, also shows ADHD-related abnormalities. The dorsal attentional network is associated with attention shifting and the control of spatial attention (32).

Visual and Motor Network

Furthermore, impairments in the visual network have been proposed (34). This network includes the visual cortex and the middle temporal area complex, both of which are connected to the dorsal attentional network. The middle temporal area complex is also functionally correlated to frontal regions, as well as to primary visual areas (5, 35).

There is also evidence that the motor network (e.g., primary motor cortex, primary sensory cortex, putamen, thalamus, and cerebellum) may be affected in ADHD (5).

Default-Mode Network

Attention deficit/hyperactivity disorder has also been conceptualized as a disorder of dysfunctional DMN activity. The DMN includes the medial prefrontal cortex (mPFC), ACC, and posterior cingulate cortex (PCC) (36). It has been suggested that in ADHD the inter-regulation between the DMN and networks activated during task performance (e.g., frontoparietal, ventral, or dorsal attentional networks) is disturbed. During task performance, DMN activity is typically suppressed. According to one hypothesis, in ADHD the DMN is hyperactive during task performance, which may cause the disruption in cognitive performance and fluctuation in attention that characterize the condition (26, 37). For example, the regulation of DMN activity by stimulant medication has been shown to improve cognitive performance in ADHD (38, 39).

Given these neurobiological functional impairments in ADHD, it seems rational to employ principles of neuroscience in treatment, which we discuss next.

MINDFULNESS-BASED COGNITIVE THERAPY FROM A NEUROPSYCHOTHERAPEUTIC PERSPECTIVE

A promising approach to improve the outcome of therapy in ADHD involves the neuropsychotherapeutic administration of meditation practice in MBCT. MBCT combines methods of cognitive behavioral therapy with mindfulness meditation. The treatment aims to provide the patient with an explanation for his symptoms, as well as information about ADHD. Behavioral interventions are designed to develop planning skills such as time management or problem solving. With cognitive methods, patients learn to identify and modify problematic thinking patterns (40). Besides cognitive behavioral interventions, patients engage in mindfulness meditation, which can be defined as a form of mental training that can improve neuropsychological deficits in ADHD, such as attention control and emotion regulation, by strengthening the function of brain regions believed to underlie these deficits (19).

It has been proposed that mindfulness meditation can help reduce mind wandering and distractibility in ADHD by improving the functioning of the DMN. For example, experienced meditators show reduced activation of the DMN during meditation and stronger functional connectivity of brain regions implicated in cognitive control and self-monitoring (41).

A further possible beneficial effect of mindfulness meditation in ADHD is that it teaches patients not to act out but rather to observe emotional states as temporary and passing events, thereby helping patients to improve their regulation of emotion. Emotion regulation refers to strategies that help to exert influence on the occurrence, experience, and expression of emotions (19, 42). Even though emotional dysregulation is not a core diagnostic feature of ADHD, it often contributes to considerable impairment (43–45). Neuroimaging studies have found neuroplastic changes in the structure and function of brain regions supporting emotion regulation (19).

The neurobiological mechanism of mindfulness meditation is currently not fully understood. It has been hypothesized that mindfulness meditation changes brain structure and function by myelinogenesis, synaptogenesis, dendritic branching, or adult neurogenesis (19). Furthermore, it seems possible that mindfulness meditation has a positive effect on neuronal preservation, restoration, and/or inhibition of apoptosis (46–48).

Besides these findings from neuroimaging studies, treatment studies have provided promising preliminary support for the feasibility and acceptability of mindfulness meditation in the treatment of ADHD. Recent studies indicate that mindfulness meditation training has ameliorating effects on ADHD symptoms and improves executive functioning, as well as emotion regulation (ISRCTN12722296 in preparation) (49, 50). Furthermore, participants show notable levels of compliance and report a high degree of satisfaction with the treatment (51). In addition, mindfulness meditation is a core component of a modified Dialectical Behavior Therapy group program for adults with ADHD. Mindfulness meditation seems to be well accepted by the patients and a very useful component of the program (52, 53) (see **Table 1**).

Given this evidence, we conclude that engagement in mindfulness meditation is associated with functional changes in brain areas suggested to be impaired in adults with ADHD. In addition, patients readily accept mindfulness meditation. Thus, mindfulness meditation appears to be a promising neurobehavioral intervention, with several potential pathways to improving neuropsychological functioning in patients with ADHD.

LIMITATIONS AND IMPLICATIONS FOR FUTURE RESEARCH

There is emerging evidence that mindfulness meditation ameliorates ADHD symptoms and may cause neuroplastic changes in brain regions impaired in ADHD. However, the study of the neurobiological mechanisms of mindfulness meditation and its beneficial effects in ADHD is still in its infancy. This allows only speculative statements about possible future treatment directions. The following limitations have to be considered, along with recommendations arising out of them.

Research is needed that uses larger sample sizes, active control conditions, and longitudinal, randomized research designs (19, 51).

To our knowledge, no neuroimaging study has investigated the effects of mindfulness meditation on the adult ADHD brain. Future research should aim to expand understanding of the neurobiological effects of mindfulness meditation in ADHD and to connect neuroscientific findings with behavioral data.

Furthermore, it has been suggested that ADHD is a heterogeneous condition, which probably includes different diagnostic subtypes (54), possibly caused by different neurobiological impairments. In addition, owing to the high comorbidity with other psychiatric disorders, common comorbid psychiatric disorders may rely on the same dysfunctional neuronal mechanisms as ADHD does. For example, ADHD and bipolar disorder show an overlap in diagnostic criteria, such as inattention and irritability (55). Also, a significantly higher prevalence of ADHD among relatives of persons with bipolar disorder and a significantly higher prevalence of bipolar I disorder among relatives of persons with ADHD has been reported (56). This co-occurrence may be associated with impairments in the same underlying neuronal mechanisms. Knowledge of these underlying neuronal mechanisms could help in developing a more specific assessment and classification of psychiatric disorders, as well as improved treatment interventions.

Another area for future research is investigation of the optimum amount of mindfulness meditation practice in ADHD. Neurobehavioral interventions are known to involve intense, prolonged, and regular stimulation of the targeted brain areas to effectively change neuronal structures (21). However, it is as yet not known how much mindfulness meditation is needed to evoke changes in neuroplasticity and psychological functioning in

TABLE 1 | Evidence of changes after mindfulness meditation.

Reference	Sample	Mean age	Duration	Results	
Neuroimaging studies					
(58)	Experienced mindfulness meditators/ non-meditators	33.8	Meditators had 7.9 years of experience	Enhanced activation during meditation	Anterior cingulate cortex (ACC) (self-regulation of attention and emotion)
(47)	Students (integrative body-mind training vs. relaxation training)	21.5	5 days, 20 min a day	Greater activation of the ventral and/ or rostral ACC during resting state after meditation	
(47)				Enhancement of the caudate nucleus and putamen during resting state following mindfulness meditation	Striatum (regulation of attention and emotion)
(41)	Experienced mindfulness meditators vs. healthy non-meditators	50.5	10 years experience	Reduced activation of the DMN during meditation Stronger functional connectivity of: posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortices	Default-mode network (brain network that is active in the resting state and inactive during task performance)
(59)	Healthy participants	26	6 weeks, 1066 min practice in total	Enhanced dorsolateral PFC activation during an emotional Stroop task	Prefrontal cortex (PFC) (attention and emotion)
(60)	Patients with general anxiety disorder vs. healthy controls	37.9	8-week program, once weekly, teacher-led group meetings plus one "day of mindfulness" in the sixth week of the course	Greater dorsolateral and dorsomedial PFC activation when participants were engaging in a mindful state while expecting to see negative emotional images	
Clinical studies					
(50)	Patients with ADHD	39.5	12 weekly sessions of 3 h MBCT, at-home practice	Reduced hyperactivity/impulsivity, as well as improved attention control	
(61)	Patients with ADHD	48.5	8 weekly sessions of 2.5 h of mindfulness training and daily at-home practice	Improvements in self-reported ADHD symptoms, anxiety and depression, improved performance on tasks measuring attention and cognitive inhibition	
(49)	Patients with ADHD	40.5	8 weekly sessions of 2.5 h of mindfulness training and daily at-home practice	Improved self-reported ADHD symptoms and improvement in executive functioning and in measured clinical ratings of ADHD symptoms	

ADHD. For example, a study in a non-ADHD sample compared the effects of an 8-week mindfulness training course in a high- vs. low-practice group. The results indicate that high engagement in mindfulness (total time practice over 8 weeks: $M = 11$ h, SD = 7 h) compared to low engagement in mindfulness (total time practice over 8 weeks: $M = 2.5$ h, SD = 1 h) is associated with improved working memory control and improved positive affect (57).

Although studies indicate that mindfulness meditation has positive effects on ADHD in adulthood, the exact working mechanisms of mindfulness meditation are unclear. For example, patients may learn to relate and react more functionally to their thoughts thanks to mindful awareness of their cognitions, or to decenter from thoughts and view them as passing events that do not have to be acted upon. Furthermore, it is possible that mindfulness meditation causes changes in other areas of life, such as better self-care (e.g., improved diet, regular exercise), which could contribute to improved treatment outcomes.

CONCLUSION

Attention-deficit/hyperactivity disorder, in adulthood is a serious mental condition with a strong neurobiological component that causes a wide range of impairments in affected individuals. Psychopharmacological medication is the first-line treatment for ADHD. However, not all patients respond well to it, and others have a preference for non-psychopharmacological treatment. Healthy psychological functioning in ADHD seems to rely greatly on the well-coordinated functioning of neuronal networks. There is promising preliminary evidence that mindfulness meditation employed as a neurobehavioral intervention in therapy can help ADHD patients to regulate impaired brain functioning and thereby improve self-regulation of attention and emotion control.

AUTHOR CONTRIBUTIONS

KB: literature research and writing, AL: literature research and writing, AP: literature research and writing, supervision.

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Conflict of Interest Statement: AP (MD) declares that she has served on advisory boards, given lectures, performed phase three studies, or received travel grants within the last 3 years from Eli Lilly and Co., Lundbeck, MEDICE Arzneimittel Pütter GmbH and Co. KG, Novartis, Servier, and Shire; and has authored books and articles on psychotherapy published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, and Springer. KB declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. AL (MD) declares that she received travel grants within the last year from MEDICE Arzneimittel Pütter GmbH and Co. KG.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 12 January 2016
doi: 10.3389/fpsyt.2015.00186

Cognitive Enhancement Therapy Improves Frontolimbic Regulation of Emotion in Alcohol and/or Cannabis Misusing Schizophrenia: A Preliminary Study

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OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Matthias Kirschner, Zurich University Hospital for Psychiatry, Switzerland
Marc Vogel, Psychiatric University Clinics Basel, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *23 October 2015*
Accepted: *21 December 2015*
Published: *12 January 2016*

Citation:
Wojtalik JA, Hogarty SS, Cornelius JR, Phillips ML, Keshavan MS, Newhill CE and Eack SM (2016) Cognitive Enhancement Therapy Improves Frontolimbic Regulation of Emotion in Alcohol and/or Cannabis Misusing Schizophrenia: A Preliminary Study. Front. Psychiatry 6:186. doi: 10.3389/fpsyt.2015.00186

Individuals with schizophrenia who misuse substances are burdened with impairments in emotion regulation. Cognitive enhancement therapy (CET) may address these problems by enhancing prefrontal brain function. A small sample of outpatients with schizophrenia and alcohol and/or cannabis substance use problems participating in an 18-month randomized trial of CET (n = 10) or usual care (n = 4) completed posttreatment functional neuroimaging using an emotion regulation task. General linear models explored CET effects on brain activity in emotional neurocircuitry. Individuals treated with CET had significantly greater activation in broad regions of the prefrontal cortex, limbic, and striatal systems implicated in emotion regulation compared to usual care. Differential activation favoring CET in prefrontal regions and the insula mediated behavioral improvements in emotional processing. Our data lend preliminary support of CET effects on neuroplasticity in frontolimbic and striatal circuitries, which mediate emotion regulation in people with schizophrenia and comorbid substance misuse problems.

Keywords: schizophrenia, alcohol misuse, cannabis misuse, emotion regulation, brain, cognitive enhancement therapy

INTRODUCTION

Substance misuse among individuals with schizophrenia is substantially higher compared to the general population (1, 2), which has been linked to problems in emotion dysregulation (3–5), defined as the inability to tolerate and appropriately manage emotions, particularly negative affects. Individuals with schizophrenia who misuse substances tend to function worse in the community (6), experience lower quality of life (7), treatment non-adherence (8, 9), and have higher rates of relapse often leading to emergency room contact and/or hospitalization (10). Indeed, the experience of overall greater severity of the illness in this population often results in two to three times more hospitalizations than patients with schizophrenia who do not abuse substances (11). Misuse of substances has been proposed to exacerbate symptoms (12), such that positive symptoms tend to be particularly more severe in people with schizophrenia and comorbid substance misuse diagnoses (13). Cannabis and alcohol have been indicated to be the two most commonly misused substances

among individuals with schizophrenia (2). While literature on the relationship between substance misuse and cognitive functioning in schizophrenia have been mixed and difficult to interpret (14), generally it can be inferred that individuals with schizophrenia who misuse alcohol or cannabis experience cognitive deficits (15, 16). In a recent randomized-controlled trial, we found that cognitive enhancement therapy [CET (17)] resulted in significant improvements in emotion regulation abilities among people with schizophrenia and alcohol and/or cannabis use problems, as well as significant reductions in alcohol use (18). CET is a psychosocial cognitive remediation intervention (19) that integrates 60 h of computer-based training targeted at improving attention, memory, and problem solving with 45 structured social-cognitive group sessions designed to improve abilities, such as perspective taking, social context appraisal, and emotion regulation abilities. Examination of the neurobiological underpinnings of improved emotion regulation associated with cognitive remediation can yield important information about the plasticity of neural mechanisms that can support addiction and psychiatric recovery in this population.

The affect regulation model has been one of the most empirically supported conceptualizations of the nature of high rates of substance misuse among individuals with schizophrenia (3, 5). This model proposes that individuals with schizophrenia who are high in trait negative affect are more likely to misuse substances as a way to cope and regulate the intensity of negative emotional states (3, 4). In support of this model, numerous studies have found that people with schizophrenia report that they misuse substances to relieve or buffer dysregulated negative emotions (20, 21). The brain circuitry for supporting successful emotion regulation involves regions in the prefrontal cortex, limbic system, and the striatum (22–24), which are also regions thought to be impacted by the pharmacological effects of addiction (25) and the symptoms of schizophrenia (26). For example, dysfunctional communication between the nucleus accumbens, frontal cortex, and hippocampus observed in non-substance abusing schizophrenia patients is similar to the substance abuse-related neurobiological changes observed in primary additive disorders (26).

Based on the aforementioned findings, we posit that participation in cognitive remediation interventions may alter functioning of the frontal, limbic, and striatal neurocircuitry to support improvement in emotion regulation in individuals with schizophrenia and substance misuse comorbidity. Meta-analytic evidence is supportive of neuroplasticity or "brain changing" effects of cognitive remediation interventions, where individuals with schizophrenia have demonstrated increased brain function in prefrontal, limbic, and striatal regions following treatment (27). Additionally, protection against gray matter loss in limbic regions has been observed in early course schizophrenia outpatients treated with CET (28). Both increased neural activation and gray matter in frontolimbic and striatal regions were associated with improved cognitive and socioemotional outcomes (27, 28). Although substance misuse is often an exclusion criterion in cognitive remediation trials (29), such findings suggest that these treatments, such as CET, may have the ability to strengthen neurobiological functions that govern emotional circuitry in individuals with schizophrenia and substance misuse comorbidity (29). However, no study has examined the neurobiological effects of cognitive remediation in people with schizophrenia who misuse substances.

Identifying biomarkers of therapeutic mechanisms in the treatment of individuals with schizophrenia is imperative for the continued understanding of the pathophysiology of the illness and the impact of substance misuse. More importantly, understanding the neurobiological effects of cognitive remediation could reinforce the utility of such interventions (19) to intervene with the diversity of challenges people with schizophrenia face, including substance misuse. Therefore, this preliminary study sought to explore the posttreatment neurobiological impact of CET on frontolimbic and striatal brain functioning during the effortful regulation of emotion in a small sample of individuals with schizophrenia who misuse alcohol and/or cannabis, the two most commonly abused substances in this population (2). The degree to which posttreatment brain functioning during emotion regulation was related to longitudinal behavioral improvements in emotion processing was also investigated.

MATERIALS AND METHODS

Participants

A total of 14 individuals diagnosed with schizophrenia ($n = 10$) or schizoaffective disorder ($n = 4$) and alcohol and/or cannabis misuse problems were included in an 18-month randomized feasibility study (NCT01292577) of CET compared to treatment as usual [TAU (18)]. All participants provided written informed consent prior to their participation. The study protocol was approved by the University of Pittsburgh Institutional Review Board, was reviewed annually, and was registered in the national clinical trials database. There were 31 participants included in the larger randomized feasibility trial of CET (18), with 14 subjects ($n = 10$ CET and $n = 4$ TAU) available for functional magnetic resonance imaging (fMRI) after completing treatment. The reasons for participants being unavailable for scanning included withdrawing consent ($n = 5$), incarceration ($n = 1$), cocaine abuse ($n = 1$), symptom instability ($n = 4$), heroin dependence ($n = 1$), lack of interest in being scanned ($n = 2$), unable to contact ($n = 2$), and ferromagnetic objects in the body ($n = 1$). Inclusion criteria for the participants were (1) age between 18 and 60, (2) diagnosis of schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for the DSM-IV [SCID (30)], (3) presentation of significant cognitive and social disability on the Cognitive Styles and Social Cognition Eligibility Interview (31), (4) an Addiction Severity Index (32) score of moderate or higher (≥4) addiction severity for cannabis or alcohol use, (5) stabilization on antipsychotic medications, (6) an IQ ≥ 80, (7) the ability to speak and read fluent English, (8) no current cocaine, amphetamine, or opioid abuse or dependence, (9) not receiving substance abuse pharmacotherapies (e.g., naltrexone), (10) no significant cognitive impairment caused by the presence of a persistent medical condition, (11) no persistent suicidal or homicidal behavior, and (12) free of any MRI contraindications.

See **Table 1** for a full description of participant characteristics. Overall, participants with fMRI data had an average age of 38.71 (SD = 13.26) years, were ill for an average duration of 14.93 (SD = 10.38) years, and completed 14.50 (SD = 1.61) years of education. Eighty-six percent ($n = 12$) of the participants also had a comorbid alcohol and/or cannabis misuse diagnosis based on the SCID (30). Two participants did not meet SCID criteria for a comorbid alcohol and/or cannabis misuse diagnosis, but met for the inclusion criteria of an Addiction Severity Index (32) score of moderate or higher (≥4) addiction severity for cannabis or alcohol use. The participants were ethnically diverse (seven Caucasian, six African American, and one Asian) and a little more than half were male ($n = 8$, 57%). Although the majority of the participants had some college education ($n = 11$, 79%) and most were not employed ($n = 11$, 79%) at the time of baseline assessment. Participants randomized to either CET ($n = 10$) or TAU ($n = 4$) did not significantly differ with regard to the above demographic variables (all $p > 0.271$), baseline IQ ($p = 0.541$), BPRS total score ($p = 0.258$), antipsychotic medication dose ($p = 0.464$), type of antipsychotic mediation (0.505), or adherence to antipsychotic medication ($p = 1.00$). The observation of a non-significant difference between CET and TAU participants with regard to type of antipsychotic medication is important given that typical and atypical antipsychotics may impact brain functioning differently (33). The CET participants were non-significantly older than the TAU participants, and there were more Caucasian participants in the CET group ($n = 6$, 60%) compared to only one (25%) Caucasian participant in the TAU group. Consequently, age and race were included as confounding covariates in all analyses of the differential effects of CET compared to TAU on brain function.

Emotional Faces *n*-Back Task

Brain functioning during the effortful regulation of emotion was elicited using an emotional faces *n*-back task, which is a modified version of the standard working memory *n*-back task including 0-back and 2-back working memory conditions (34). An *n*-back

TABLE 1 | Baseline characteristics of CET and TAU participants with schizophrenia who misuse alcohol and/or cannabis presented as *N* (%) or *M* (SD).

Characteristic	Total ($n = 14$)	CET ($n = 10$)	TAU ($n = 4$)	p^a
Age (years)	38.7 (13.26)	41.20 (13.65)	32.50 (11.45)	0.285
Sex (male)	8 (57%)	6 (60%)	2 (50%)	1.00
Race: Caucasian	7 (50%)	6 (60%)	1 (25%)	
African-American	6 (43%)	4 (40%)	2 (50%)	0.271
Asian	1 (7%)	–	1 (25%)	
IQ	101.43 (11.69)	102.70 (13.6)	98.25 (4.27)	0.541
Attended college	11 (79%)	8 (80%)	3 (75%)	0.728
Education (years)	14.50 (1.61)	14.6 (1.65)	14.25 (1.71)	1.00
Not employed	11 (79%)	7 (70%)	4 (100%)	0.505
Illness length (years)	14.93 (10.38)	15.50 (10.52)	13.5 (11.45)	0.759
BPRS total	42.93 (10.26)	40.90 (7.77)	48.0 (15.08)	0.258
ASI: alcohol	4.5 (2.68)	4.40 (3.10)	4.75 (1.50)	0.835
ASI: drug	3.14 (2.14)	3.0 (2.49)	3.50 (1.00)	0.710
Principle diagnosis				
Schizophrenia	10 (71%)	8 (80%)	2 (50%)	
Schizoaffective	4 (29%)	2 (20%)	2 (50%)	0.520
Substance abuse or dependence diagnosis	12 (86%)	9 (90%)	3 (75%)	0.505
Alcohol dependence	7 (50%)	5 (50%)	2 (50%)	1.00
Alcohol abuse	2 (14%)	2 (20%)	–	1.00
Cannabis dependence	7 (50%)	5 (50%)	2 (50%)	1.00
Cannabis abuse	1 (7%)	–	1 (25%)	0.286
Daily substance use among active users				
Alcohol use occasions per day	2.15 (2.39)	2.59 (2.42)	1.07 (2.14)	0.301
Cannabis use occasions per day	0.34 (0.85)	0.48 (0.98)	–	0.363
Antipsychotic medication				
Atypical	11 (79%)	7 (70%)	4 (100%)	0.505
Typical	3 (21%)	3 (30%)	–	
Dose (CPZ equivalent)	449.52 (360.69)	402.67 (370.68)	566.67 (354.86)	0.464
Adherent	13 (93%)	9 (90%)	4 (100%)	1.00
MSCEIT total score				
Baseline	87.33 (14.98)	85.94 (14.27)	90.82 (18.40)	0.602
Posttreatment	91.17 (15.53)	92.19 (14.98)	88.61 (18.96)	0.713
ER-40 correct response				
Baseline	32.29 (3.45)	31.90 (3.96)	33.25 (1.71)	0.530
Posttreatment	33.18 (3.05)	33.35 (3.54)	32.75 (1.50)	0.754

ASI, Addiction Severity Index; BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine, MSCEIT, The Mayer–Salovey–Caruso Emotional Intelligence Test; ER-40, Penn Emotion Recognition Test-40.

[a]Results from independent sample t-tests or Fisher's exact tests, two-tailed.

task is one that asks participants to respond when they view a stimulus (e.g., letter) that is the same as that presented *n* trails previously. In addition to the working memory conditions (0-back and 2-back), four emotional valence distracter conditions (no faces, happy faces, fearful faces, and neutral faces) were presented to participants. Faces were flanked on each side of the *n*-back letter stimuli (**Figure 1**). The faces were from the NimStim dataset in grayscale (35), were normalized for size and luminance, and balanced by gender. Both working memory and emotional valence conditions were presented in randomized blocks of 12 trials each. By directing participants' attention to the working memory components of the task, participants were required to inhibit their response to the emotional stimuli in order to successfully complete the *n*-back tasks (36), and thus this task is considered a test of effortful emotion regulation. Each block started with instructions indicating the working memory condition (0-back or 2-back) presented on the screen for 3500 ms, which was followed by the target stimulus (letters) presented flanked by the different emotional valence distracter conditions (happy, fearful, neutral, or no face) for 500 ms, with an interstimulus interval jittered at an average of 3500 ms. The total task time was 6 min and 56 s with each emotional valence distracter condition presented once for both the 0-back and 2-back conditions. All the participants completed two runs of the emotional faces *n*-back paradigm, with the exception of one TAU participant that completed one run. Since the focus of this research was on emotion regulation during effortful cognitive processing, only data from the effortful 2-back condition were analyzed.

Image Acquisition and Processing

A 3-T Siemens Verio whole-body scanner with a 12-channel head coil was used to collect structural and functional neuroimaging data at the Scientific Imaging and Brain Research Center at Carnegie Mellon University. Functional MRI data were acquired using an echo T2*-weighted sequence with real-time motion correction (3.2 mm × 3.2 mm × 3.2 mm voxel size, TR = 2000 ms, TE = 30 ms, bandwidth = 2298 Hz/px, FOV = 205 mm, flip angle = 79°, 64 × 64 matrix, 36 slices, slice thickness = 3.2 mm).

Statistical Parametric Mapping Software, version 8 (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) was used to preprocess imaging data. The images were normalized to a common Montreal Neurological Institute (MNI) coordinate space using an indirect normalization pipeline, with parameters obtained from a high-resolution T1 structural image. Images were smoothed with an 8-mm full-width at half maximum Gaussian kernel. Signal and movement outliers were identified using the Artifact Detection Tool (37) software package and entered into each participant's first-level general linear model as regressors of no interest.

Emotion Processing Behavioral Measures

In addition to assessing brain functioning during effortful emotion regulation measured by the emotional faces *n*-back task outlined above, behavioral measures of emotion processing were also utilized in the parent study (18) to examine behavioral emotion processing skills at pre- and posttreatment. The Mayer–Salovey–Caruso Emotional Intelligence Test [MSCEIT (38)] and the Penn Emotion Recognition Test-40 [ER-40 (39)] were the measures used to assess emotion processing. Noteworthy, brain regions important for emotion processing, which includes emotion regulation, such as limbic areas, have been shown to be associated with performance on both these measures (40, 41).

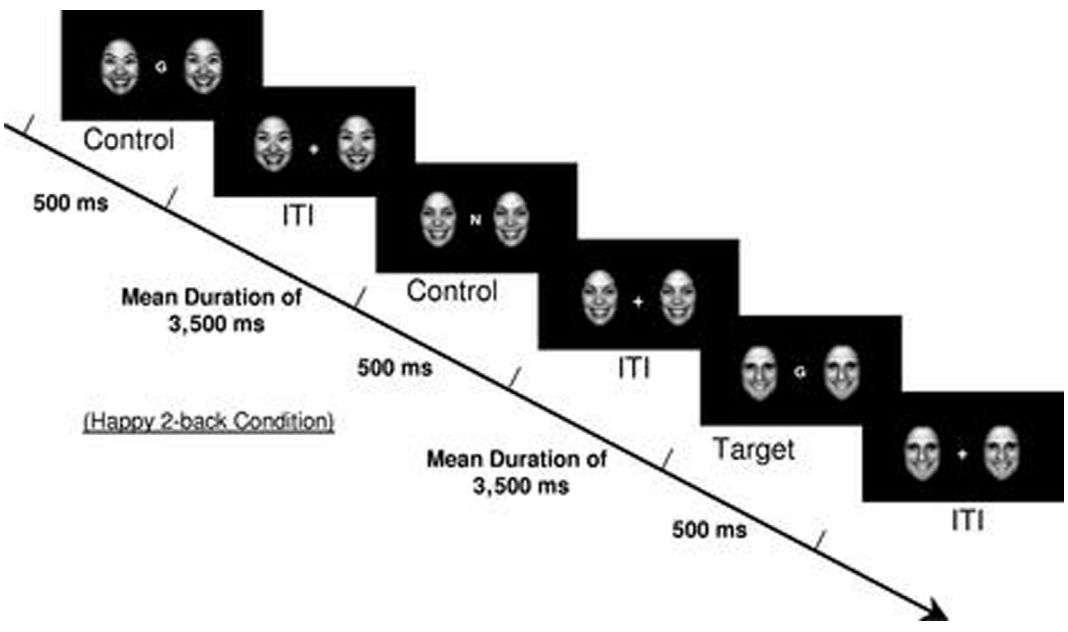

FIGURE 1 | Example of a 2-back happy face distracter condition from the emotional faces *n*-back task. [Reproduced with permission from Ladouceur et al. (34)].

The MSCEIT is a 141-item performance-based measure of emotion processing and management (e.g., emotional intelligence) that is administered on the computer (42). Performance scores are based on a large normative sample scale ($M = 100$, SD = 15), with a higher score indicating a better emotional intelligence quotient (38). The MSCEIT is a recommended measure of the National Institute of Mental Health's committee on Measurement and Treatment Research to Improve Cognition in Schizophrenia [NIMH-MATRICS (43)] and has been shown to have good reliability and sufficient construct and concurrent validity (43, 44). The ER-40 is also a frequently utilized measure of emotion processing in schizophrenia, as it has good psychometric properties (45) and is able to discriminate between healthy controls and individuals with schizophrenia (39). The ER-40 is a forced-choice, computer-administered assessment of the ability to accurately recognize different emotions. The task involves a series of 40 happy, sad, angry, fearful, or neutral (non-emotional) faces. Scores represent number of correct responses, with a higher score indicating better performance.

TREATMENTS

Medication

All participants were maintained on antipsychotic medications approved for the treatment of schizophrenia or schizoaffective disorder as prescribed by their treating psychiatrist. **Table 1** lists antipsychotic medication characteristics of the participants.

Cognitive Enhancement Therapy

Cognitive enhancement therapy is a performance-based, comprehensive, developmental approach to the remediation of social-cognitive and neurocognitive deficits in participants with schizophrenia (17). CET consists of 60 h of weekly computer-based neurocognitive training to in attention, memory and problem-solving and 45 small-group sessions to address social-cognitive deficits that limit functional recovery from schizophrenia. To encourage socialization, neurocognitive training is implemented in patient pairs and conducted with coaching from a CET therapist. One-hour neurocognitive training sessions begin with Ben-Yishay's Orientation Remediation Module (46) to improve different aspects of attention and speed of processing. Following ~3 months of attention training, 3–4 participants combine to form a social-cognitive group. The 1.5-h social-cognitive group sessions utilize experiential learning approaches to teach a wide range of social-cognitive abilities designed to enhance social wisdom and interpersonal success. Key theoretically driven components of the social-cognitive groups include perspective-taking, social gist abstraction, nonverbal communication, emotion management, and foresightfulness. The social-cognitive group curriculum encourages participants to engage in activities that include responding to unrehearsed social exchanges, presenting homework, participating in social-cognitive exercises, providing feedback to others, and leading homework review. Neurocognitive training in memory and problem-solving using PSSCogReHab (47) software proceeds concurrently with the social-cognitive groups after the conclusion of attention training. A complete description of CET has been provided elsewhere (17).

Treatment As Usual

Treatment as usual served as the comparison treatment condition in this randomized feasibility trial of CET for schizophrenia participants who misuse substances. TAU consisted of traditional social services and mental health programs, which included psychiatric services, case management, individual supportive therapy, vocational rehabilitation, dual diagnosis treatment programs, and other community-based treatments for substance use. All efforts were made to link both CET and TAU participants with necessary mental health and substance abuse services while participating in the study.

PROCEDURES

Participants were recruited from Western Psychiatric Institute and Clinic and other community clinics at Pittsburgh, PA, USA. Potential participants were screened for eligibility using the SCID (30), the Ammons Quick IQ Test (48), the Addiction Severity Index (32), and the Cognitive Style and Social Cognition Eligibility Interview (31). Those participants meeting inclusion criteria were then randomized to receive 18 months of either CET or TAU. Individuals were then assessed every 6 months using the aforementioned behavioral emotion processing measures. A subset of 14 participants ($n = 10$ CET, $n = 4$ TAU) completed posttreatment fMRI scanning. Neuroimaging assessments were only available posttreatment as part of a separate pilot study that became available near the end of the larger feasibility trial of CET for alcohol and/or cannabis misusing schizophrenia (18). See Eack et al. (18) for details on this larger feasibility trial, such as the randomization procedures and the enrollment diagram. All participants provided written informed consent prior to their participation. The study protocol was approved by the University of Pittsburgh Institutional Review Board, was reviewed annually, and was registered in the national clinical trials database (NCT01292577).

Data Analysis

Functional neuroimaging data are inherently hierarchical in nature, with brain images (collected every 2 s) nested within individuals in a time series. Analysis proceeds by first estimating the effects of task condition on brain activity for each individual (first-level analysis) and then subjecting those contrasts to group (second-level) analyses (49). SPM8 was utilized for first- and second-level voxel-based analyses to examine the differential posttreatment effects of CET compared to TAU on emotion regulation-related brain functioning. First-level analyses consisted of modeling neural responses during each condition of the emotional faces *n*-back task with general linear models in each of the participants. First-level models also included the signal and motion outliers identified by the Artifact Detection Tool as covariates (37). First-level contrasts (happy face vs. no face, fearful face vs. no face, and neutral face vs. no face) were then entered into a second-level group analysis based on a two (CET vs. TAU) × three (happy face vs. no face, fearful face vs.

no face, and neutral face vs. no face) general linear model. To control the effect of general visual stimulation, the second-level contrasts compared emotional faces to neutral faces [e.g., (happy vs. no face)–(neutral vs. no face)]. As mentioned above, second-level models included age and race as confounding covariates. A single region of interest mask was created in the Wake Forest University PickAtlas toolbox (50) with anatomical definitions provided by Tzourio-Mazoyer, Landeau (51). Regions of interest included frontolimbic and striatal areas, which were the bilateral amygdala, insula, dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex, orbitofrontal cortex, striatum, nucleus accumbens, and the anterior cingulate cortex. These regions have been repeatedly implicated in the regulation of emotion (22, 24, 36, 52). Due to the conservativeness of voxel-wise multiple comparison corrections in small samples (53), Type I error was controlled using a cluster-extent thresholding method. Cluster-level correction with a small sample may provide the best balance between type I and type II error (54). Based on 10,000 Monte Carlo simulations executed in 3dClustSim (55), type I error was indicated to be controlled at an α-level of 0.05 using a combined threshold of a voxel extent of 34 and an uncorrected p of 0.001.

Associations between differential posttreatment effects during emotion regulation-related brain functioning and changes in behavioral emotion regulation performance from pre- to posttreatment were analyzed with bivariate correlations and mediator models executed in R 3.1.2 (56). It was determined that age, race, and antipsychotic medication dose were not significantly related to emotion processing behavioral performance and emotion regulation-related brain functioning. Therefore, these variables were not included as covariates to retain statistical power in correlations and mediator models. Average magnitude estimates per region of interest per participant were extracted using MarsBar, version 0.44 [http://marsbar.sourceforge.net (57)] from the above imaging analysis to be utilized for correlation and mediation analyses. A path analysis approach was used for the mediation analysis (58), which was based on the mediator-analytic framework presented by Kraemer et al. (59) for randomized clinical trials. Mediator models were constructed with a series of linear models (60) that analyzed the indirect effects of treatment assignment (predictor) on longitudinal changes in emotion processing behavioral performance (outcome) through posttreatment emotion regulation-related brain functioning (mediator). This was accomplished by computing the association between (1) treatment assignment and emotion regulation-related brain functioning, (2) emotion regulation-related brain function and longitudinal changes in emotion processing behavioral performance, and (3) treatment assignment and longitudinal changes in emotion processing behavioral performance. Based on MacKinnon et al. (61), the magnitude and significance of the mediation effects was estimated using an asymptotic z' test of indirect effects. Logarithmic transformations were used to correct any variables with significantly skewed distributions prior to analysis, which included the left inferior orbital frontal cortex, right DLPFC (BA 46), and reaction time from the emotional faces n-back. Missing data were handled with an expectation-maximization approach (62).

RESULTS

Emotional Faces n-Back Task Performance

Reaction time and accuracy performance on the emotional faces n-back task was also analyzed in R with mixed-effects models examining group (CET vs. TAU), working memory loading (0-back vs. 2-back) and emotional distracter valence (happy vs. fearful vs. neutral vs. no faces) effects. One TAU participant had accuracy data available but did not have recorded reaction time data due to technical issues. Investigation of task performance on the emotional faces n-back task during scanning revealed that participants had neither overall high accuracy, with no significant group ($p = 0.228$) or emotional distracter valence differences ($p = 0.803$) nor were there any significant group by emotional distracter valence interactions ($p = 0.921$), group by working memory loading interactions ($p = 0.369$), or group by emotional distracter valence by working memory loading interactions ($p = 0.918$). Accuracy was high across both groups of participants, however, significantly lower for the 2-back condition (93%) compared to the 0-back condition (97%), χ^2 (1, $N = 14$) = 9.68, $p = 0.002$.

Overall, participants did not significantly differ in reaction times with regard to group assignment ($p = 0.695$). With regard to the working memory loading condition, the participants had significantly slower reaction times during the 2-back condition ($M = 6.73$ ms_{log}, SE = 0.06) compared to the 0-back condition ($M = 6.44$ ms_{log}, SE = 0.06), χ^2 (1, $N = 13$) = 72.81, $p < 0.001$. CET and TAU participants had similar reaction times during the 0-back (CET: $M = 6.44$ ms_{log}, SE = 0.05; TAU: $M = 6.42$ ms_{log}, SE = 0.10), but during the 2-back condition, the CET participants had significantly slower reaction times ($M = 6.78$ ms_{log}, SE = 0.05) compared to the TAU participants ($M = 6.68$ ms_{log}, SE = 0.10), χ^2 (1, $N = 13$) = 3.86, $p = 0.049$. Participants did neither significantly differ in reaction times with regard to emotional valence distracters ($p = 0.058$) nor were significant interactions observed for group by emotional distracter valence ($p = 0.415$) or group by emotional distracter valence by working memory loading ($p = 0.491$). Such results are confirmatory that participants were paying attention to the task and any differences in brain functioning elicited during the task are not due to differential inability to complete the task.

Posttreatment Effects of CET on Frontolimbic and Striatal Brain Functioning During Effortful Emotion Regulation

Region-of-interest voxel-based analyses were conducted using a 2 (CET vs. TAU) × 3 (happy vs. no face, fearful vs. no face, and neutral vs. no face) general linear model to investigate posttreatment brain differences between CET and TAU participants during effortful emotion regulation. No significant interaction effects were observed with regard to the emotional distracter conditions, and thus the main effects of treatment group were examined. Compared to the TAU group, CET participants

displayed significantly greater activation during the emotion regulation task in a large cluster involving the left inferior orbital frontal, insula, and ventromedial prefrontal cortices (**Table 2**; **Figure 2**). Participants treated with CET, compared to TAU, also had significantly greater emotion regulation-related activation in the right DLPFC, right anterior cingulate cortex, right putamen, bilateral caudate, and in a moderately sized cluster in the right orbital frontal and right ventromedial prefrontal cortices (**Table 2**; **Figure 2**). Accordingly, the direction of greater activation related to CET during emotion regulation in the above frontolimbic and striatal regions may be indicative that CET is contributing to neurobiological changes in people with schizophrenia and comorbid substance misuse problems.

Association Between Posttreatment Brain Functioning During Emotion Regulation and Longitudinal Improvements in Emotion Processing Behavioral Performance

Greater posttreatment activation during the effortful regulation of emotion in all regions observed to be significantly different between CET and TAU participants (**Table 2**) were significantly correlated with greater longitudinal improvements in MSCEIT total scores (all *r*'s 0.58–0.77, all $p < 0.030$), with the exception of the right DLPFC (BA 46 only). Greater longitudinal improvement on the ER-40 was significantly correlated with greater posttreatment activation in the large cluster involving the left inferior orbital frontal, ventromedial prefrontal, and insula cortices ($r = 0.56$, $p = 0.037$). Greater activation in the orbital frontal cortex (cluster including the inferior, middle, and superior levels; $r = 0.65$, $p = 0.011$) and the right DLPFC (BA 9; $r = 0.56$, $p = 0.038$) was also significantly associated with greater longitudinal improvement on the ER-40. Mediation analyses revealed that, when adjusting for treatment assignment, greater differential emotion regulation-related activation, favoring CET, in the cluster involving the left inferior orbital frontal, ventromedial prefrontal, and insula cortices, had a significant direct effect on improved total scores on the MSCEIT, with this cluster significantly mediating the association between treatment assignment and improved performance on this test (**Table 3**). No direct or mediation effects were observed with regard to changes scores on the ER-40.

DISCUSSION

Substance misuse among people with schizophrenia, especially for alcohol and cannabis (2), is a common, significant problem as addiction is associated with more severe illness trajectories (11) and worse community functioning (6). Poor emotion regulation may be a key contributor of elevating the risk for substance misuse in individuals with schizophrenia (3, 4). Neural correlates of disrupted emotion regulation in individuals with schizophrenia and substance misuse problems (52) have been shown to include frontal, limbic, and striatal regions important for emotional neurocircuitry (22, 23, 36). Recently, significant improvements in emotion regulation abilities were observed in individuals with schizophrenia who also misuse alcohol and/or cannabis after being treated with CET, a cognitive remediation intervention (18). Therefore, this original, exploratory study sought to examine differences in brain functioning during effortful emotion regulation in participants with comorbid schizophrenia and alcohol and/or cannabis misuse following CET or TAU. The direct and mediation effects of these neurobiological differences on longitudinal changes in behavioral emotion processing outcomes were also examined.

Compared to participants in TAU, CET participants displayed significantly greater activation in frontal, limbic, and striatal networks involved in the regulation of emotion at posttreatment (22–24, 36, 63), including the DLPFC, ventromedial prefrontal cortex, orbital frontal cortex, anterior cingulate, insula, caudate, and putamen. No significant interactions were observed regarding emotional valence during the emotional faces *n*-back task. Longitudinal improvements in behavioral emotion processing abilities were correlated with greater activation in the majority of these above regions. Interestingly, a mediating effect was observed in an area including the orbital frontal cortex, ventromedial prefrontal cortex, and the insula such that greater brain activation in these regions mediated longitudinal improvements in behavioral emotion processing abilities.

TABLE 2 | Differential activation during the emotional faces *n*-back task observed between CET and TAU participants at posttreatment.

Region	BA	MNI coordinates	Cluster size	*z*	*p*	Direction
L inferior orbital frontal L insula L ventromedial prefrontal	47, 13	−50 24 −4	530	4.61	<0.001	CET > TAU
R putamen/caudate	–	26 22 2	160	4.56	<0.001	CET > TAU
R inferior/middle/superior orbital frontal R ventromedial prefrontal	47	44 52 −2	91	3.73	<0.001	CET > TAU
R DLPFC	9	38 24 34	69	4.13	<0.001	CET > TAU
R anterior cingulate	10	12 52 10	43	4.67	<0.001	CET > TAU
R DLPFC	46	46 40 16	38	3.49	<0.001	CET > TAU
L caudate	–	−6 6 8	37	3.55	<0.001	CET > TAU

BA, Brodmann area; MNI, Montreal Neurological Institute; L, left; R, right; CET, Cognitive Enhancement Therapy; TAU, treatment as usual.
Presented results are corrected for multiple comparisons based on 10,000 Monte Carlo simulations executed in AlphaSim (55) using 3dClustSim (α-level of 0.05, k = 34, uncorrected p of 0.001).

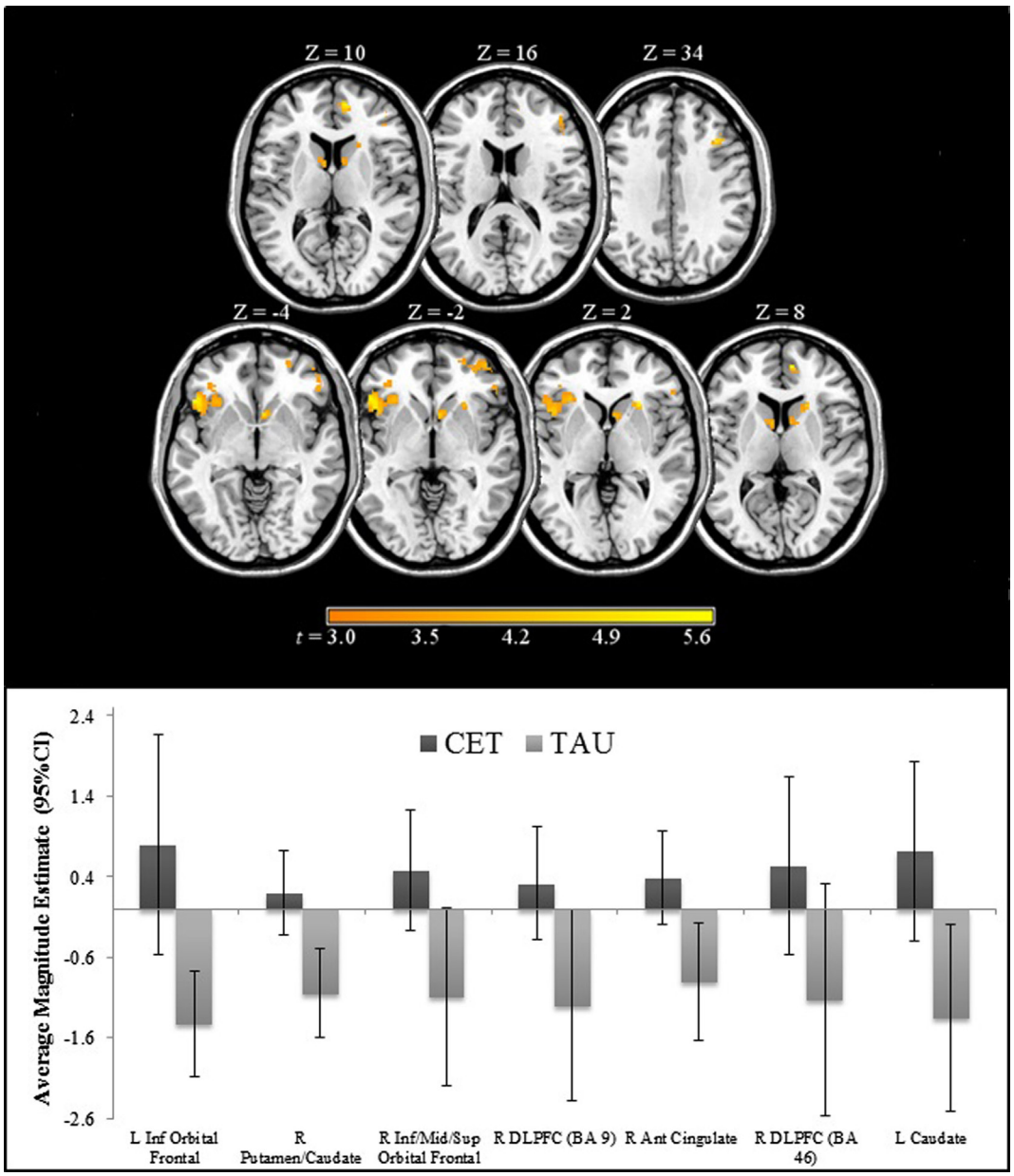

FIGURE 2 | Regions of significantly greater activation in participants completing 18 months of CET, compared to TAU, during the emotional faces *n*-back task.

Such results suggest that treatment with CET (18) may be normalizing the coordination and function of frontolimbic and striatal regions involved in emotion regulation in individuals with schizophrenia who also misuse alcohol and/or cannabis. This is evidenced by research demonstrating that communication of prefrontal and limbic regions modulates cognitive control over emotion regulation abilities (64–66), which has been observed to be dysregulated in individuals with schizophrenia (67, 68). It may be that improved cognitive functioning gained through CET (69, 70) increased participants' ability to regulate and manage their emotional states. Meta-analytic evidence has shown that cognitive remediation interventions have a common neural plasticity effect of increasing activation in frontal and limbic regions that are related to improved cognitive and socio-emotional functioning in individuals with schizophrenia (27). The findings from this investigation of increased task-related activation in some overlapping frontolimbic regions are supportive of CET as an effective intervention for supporting functional recovery of this underserved, vulnerable population.

Of course, these findings have many caveats that preclude firm conclusions regarding causality of treatment efficacy. The

TABLE 3 | Relationships between posttreatment emotion regulation brain functioning and longitudinal changes in behavioral emotion processing performance.

	Direct effect					Mediator effect
Regional clusters	***B***	**SE**	***t***	**df**	***p***	***z′***
	ΔMSCEIT total score					
L inferior orbital frontal						
L insula	14.3	4.3	3.3	11	0.007	−2.7**
L ventromedial prefrontal						
R putamen/caudate	5.6	3.0	1.9	11	0.086	−1.7+
R inferior/middle/superior orbital frontal	3.1	2.1	1.5	11	0.169	−1.2
R ventromedial prefrontal						
R DLPFC (BA 9)	3.7	2.2	1.7	11	0.116	−1.4
R anterior cingulate	4.3	2.8	1.5	11	0.155	−1.4
R DLPFC (BA 46)	1.4	5.9	0.2	11	0.813	−0.2
L caudate	2.8	1.4	2.1	11	0.062	−1.8+
	ΔER-40 correct responses					
L inferior orbital frontal						
L insula	1.6	1.3	1.2	11	0.251	−1.2
L ventromedial prefrontal						
R putamen/caudate	0.4	0.8	0.6	11	0.578	−0.6
R inferior/middle/superior orbital frontal	0.9	0.5	2.0	11	0.072	−1.6
R ventromedial prefrontal						
R DLPFC (BA 9)	0.7	0.5	1.3	11	0.206	−1.1
R anterior cingulate	0.2	0.7	0.3	11	0.764	−0.3
R DLPFC (BA 46)	1.4	1.3	1.1	11	0.292	−0.9
L caudate	0.3	0.4	0.8	11	0.443	−0.8

L, left; R, right; DLPFC, dorsal lateral prefrontal cortex; MSCEIT, The Mayer–Salovey–Caruso Emotional Intelligence Test; ER-40, Penn Emotion Recognition Test-40.
***$p < 0.01$.*
+$p < 1.00$.

first limitation is the very small sample size employed in this research, particularly in the TAU condition. This may explain the lack of significant emotional valence interactions with group assignment from the emotional faces *n*-back task, although sufficient power was available to detect the very large effects observed in frontolimbic brain functioning. Also related to the small sample size, the groups were not perfectly matched especially with regard to age and race. Although age and race were not significantly different between the groups, we did include them as possible confounders in all analyses examining differential effects of treatment on brain functioning. Noteworthy, CET had a higher, but non-significantly different attrition rate compared to TAU in the larger feasibility trial [for a further description, see Eack et al. (18)]. Next, because the imaging component was an opportunistic add-on study funded near the completion of the parent clinical trial, no pretreatment imaging data were available. Posttreatment randomized-controlled trials are common and protect against many threats to internal validity (71), but in the case of quantitative outcomes with unknown baseline values, they are unable to determine the magnitude of change. We suspect that the greater brain activation observed in CET during emotion regulation is reflective of longitudinal increases in frontolimbic activity. However, in the absence of an active comparison group, such findings may also reflect nonspecific CET effects associated with more therapeutic contacts, including group activities. Further, retention of participants for fMRI procedures was greater in CET than TAU, which may have impacted the results by limiting the sample of TAU participants. However, there were no significant differences in baseline characteristics observed between TAU participants who did vs. did not complete an fMRI scan ($p > 0.166$). In addition, we did not assess participants level of alcohol and/or cannabis use at the time of posttreatment scanning or during assessments of emotion processing, which could have influenced brain functioning and performance. It will be important for future studies to employ longitudinal imaging methods and assess substance misuse at the time of assessments to address these issues, and until these findings can be replicated in adequately powered samples they should be considered tentative and interpreted with caution. It will also be important for future research with larger sample sizes to examine the implications of such findings on symptom severity and other functional outcomes in the illness.

In summary, this preliminary study was the first to show a possible neural plasticity relationship between CET and emotion regulation-related brain functioning in individuals with schizophrenia and alcohol and/or cannabis misuse comorbidities participating in a randomized clinical trial. The findings indicated that CET may lead to differential changes in functioning of frontolimbic and striatal regions implicated in the regulation of emotion. Increased activation in these regions during effortful emotion regulation was supportive of longitudinal improvements in behavioral emotion processing abilities. Improved emotion regulation may serve as a protective factor for substance misuse as well as play a role in improved interpersonal and other psychosocial functioning. The findings from this investigation are not only informative for future research but also highlight the utility of providing cognitive remediation interventions, such as CET, to optimize recovery for people with schizophrenia who have substance misuse problems, particularly for alcohol and cannabis.

AUTHOR CONTRIBUTIONS

JW, SH, JC, MP, MK, CN, and SE all made substantial contribution to this manuscript.

FUNDING

Funding for this research was provided by NIH grants DA-30763 (SE), MH-95783 (SE), and RR-24154 (SE).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

PERSPECTIVE
published: 27 January 2016
doi: 10.3389/fpsyt.2016.00007

Can We Use Neurocognition to Predict Repetition of Self-Harm, and Why Might This Be Clinically Useful? A Perspective

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Over 800,000 people die by suicide each year globally, with non-fatal self-harm 20 times more common. With each episode of self-harm, the risks of future self-harm and suicide increase, as well as personal and healthcare costs. Therefore, early delineation of those at high risk of future self-harm is important. Historically, research has focused on clinical and demographic factors, but risk assessments based on these have low sensitivity to predict repetition. Various neurocognitive factors have been associated with self-harming behavior, but it is less certain if we can use these factors clinically (i) as risk markers to predict future self-harm and (ii) to become therapeutic targets for interventions. Recent systematic reviews and meta-analyses of behavioral tasks and fMRI studies point to an emerging hypothesis for neurocognition in self-harm: an underactive pre-frontal cortex is unable to respond appropriately to non-emotional stimuli, or inhibit a hyperactive emotionally-/threat-driven limbic system. However, there is almost no imaging data examining repetition of self-harm. Extrapolating from the non-repetition data, there may be several potential neurocognitive targets for interventions to prevent repeat self-harm: cognitive training; pharmacological regimes to promote non-emotional neurocognition; or other techniques, such as repetitive transcranial magnetic stimulation. Hence, there is an urgent need for imaging studies examining repetition and to test specific hypotheses. Until we investigate the functional neurocognitive basis underlying repetition of self-harm in a systematic manner using second-generational imaging techniques, we will be unable to inform third-generational imaging and potential future clinical applications.

Keywords: self-harm, neurocognition, functional magnetic resonance imaging, structural magnetic resonance imaging, risk prediction, suicide, cognitive tasks

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Johannes Sebastian Wrege, Psychiatric Clinic of University of Basel (UPK), Switzerland
Kees Van Heeringen, Ghent University, Belgium

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *02 December 2015*
Accepted: *11 January 2016*
Published: *27 January 2016*

Citation:
de Cates AN and Broome MR (2016) Can We Use Neurocognition to Predict Repetition of Self-Harm, and Why Might This Be Clinically Useful? A Perspective. Front. Psychiatry 7:7. doi: 10.3389/fpsyt.2016.00007

SELF-HARM AND RISK ASSESSMENT FOR PREDICTION OF ITS REPETITION

What Is Self-Harm and Why Is It Important?

Self-harm, where an individual intentionally causes physical harm to themselves by self-injury or self-poisoning irrespective of motivation (1, 2), affects both those with and without previously diagnosed mental illness. Any episode of self-harm potentially results in (i) serious morbidity or

(ii) death by suicide. Studies suggest that between one in 20 and one in 40 self-harm episodes with reported intent to die ends in completed suicide (3–5). Globally, over 800,000 people die by suicide annually (6–8), and it is estimated that by 2020, suicide will contribute more than 2% to the global burden of disease (9). In the UK, and internationally, the total number of suicides in the general population has been rising since 2009 (8, 10, 11) with this rise most marked in men aged 45–54 years (10). However, self-harm and suicide remain important throughout the lifespan: suicide is the second most common cause of death in young people in the UK (12) with a conservative estimate of 10% of young people reporting at least one episode of self-harm (13).

Historically, the over-arching term "self-harm" has been divided into "parasuicide" (no reported intention from the individual concerned to die) and "attempted suicide" (where there is a reported intention to die). However, reported intent of previous episodes of self-harm does not appear to correlate with future self-harm or suicide (14–16). This may be because of conscious or subconscious underreporting by the individual, or it may be because the pathophysiology of self-harm and the potential future pathway is the same regardless of previous conscious intent. For this reason, both the World Health Organization (WHO) and the UK National Institute of Health and Care Excellence (NICE) include all behavior regardless of method or intent in their definitions of self-harm (1, 2). However, intent remains used as a delineating factor particularly in the US to separate non-suicidal self-injury (NSSI) from suicidal attempts, which are then treated separately for clinical and research purposes. However, recent research shows that self-harm method switching occurs routinely in individuals (17). If, in fact, this dichotomy is false, by separating out self-harm on presumed or purported intent or method used we may be reducing the number of available participants for studies into self-harm.

How Have Predictors of Self-Harm Been Approached and Analyzed?

Prevention of suicide remains difficult, partly because the complex underlying cognitive processes remain only partially understood (18, 19). The few successful prevention strategies have appeared to focus on public health level interventions, such as paracetamol sale restrictions (20). Suicide prevention is in need of markers that predict future self-harm and serve as a basis for intervention (21). To date, self-harm research has focused on retrospective identification of high-risk individuals following self-harm using demographic and clinical factors, e.g., age, sex, diagnosis of mental illness (22–25). This is because this information is easily achievable from patient records rather than requiring direct patient contact (26, 27), which is more difficult, costly, and has many ethical implications. However, the increasing suicide rate of late despite our improved understanding of demographic and clinical factors indicates that these factors are inadequate in terms of predicting future risk of self-harm alone. Standard risk assessment tools based on these factors, such as the SADPERSONS tool, do not appear to accurately predict individuals requiring psychiatric admission or community aftercare, or to predict those who repeat self-harm (28). Furthermore, the 2014 UK confidential inquiry report on suicides in primary care found that 37% of those who died by suicide between 2002 and 2011 did not have a mental health diagnosis recorded on their GP records (11). This reinforces the fact that to prevent suicides we need to learn how to identify high-risk people in those not previously known to mental health services or with known mental illness.

What Is Already Known about Predicting Repetition of Self-Harm?

There is almost ubiquitous evidence that the most important predictor of future self-harm is past self-harm (14, 29–31). After a first episode of self-harm, approximately one in six patients repeats self-harm over the first year, and one in four after 4 years (14). With repetition, there is an increasing risk of suicide (32) and increased costs personally and to the health service (33). Therefore, the study of prediction of repetition of self-harm is very important to try and reduce the personal, clinical, social, and financial burdens of self-harm and suicide.

Repetition of self-harm has been associated with various demographic and clinical factors, including (i) sociodemographics [extremes of age, and low educational level (30, 34), being unmarried (35), and being unemployed (36)]; (ii) personal history [abuse in childhood (37)]; and (iii) specific mental disorder diagnosis [personality disorder (38), anxiety disorder (39), depression (27), and substance and alcohol misuse (40, 41)]. However, although up to 90% of people who die by suicide have a psychiatric disorder (42), making this a risk factor for self-harm, most people with a mental illness will not self-harm. Thus, psychiatric diagnosis is not very helpful in terms of predicting suicide or why an individual might do so (19). The most commonly used risk assessment tool in England based on clinical and demographic factors, the SADPERSONS tool (43), does not accurately predict individuals requiring psychiatric admission or community aftercare, or repeat self-harm (28).

Why Is Repetition of Self-Harm Particularly Important?

In the longer term, it appears possible that repetition of self-harm in young people may act as a marker of an emerging wider psychopathological process, resulting in long-term contact with mental health services and need for care. The self-harm itself may or may not persist (44, 45), but young people who self-harm repeatedly appear at greater risk of serious mental illness and poor educational and occupational outcomes in later adulthood (45). Therefore, a greater understanding of repeat self-harm, and its neurobiological basis, is vital to be able to both predict and prevent suicide, but also to alleviate current and long-term mental distress, and to aid early detection of young people at high risk of future psychiatric difficulties.

NEUROBIOLOGICAL BASIS FOR NEUROCOGNITION IN SELF-HARM

Self-Harm as a Complex Clinical Syndrome at Least Partly Independent of, but Influenced by, Diagnosis

Prediction of future risk of self-harm is likely to be enhanced if this non-individualized data (demographic and clinical factors)

could be combined with more personalized individual-based factors, such as personality and cognition. Self-harm is likely to be best understood as an interaction between underlying individual susceptibilities to self-harm (such as personality and cognitive factors) and current social and health stressors (such as employment or financial issues, mental and physical illness, and negative life events), known as a "stress–diathesis model" (18, 19, 46, 47). Various stress–diathesis models of self-harm exist, typically based on the concept that self-harm may represent a clinical syndrome in its own right (19, 47, 48). This is consistent with recent National Institute of Mental Health guidance in the US which has reported that it will only commission and fund future research if it crosses existing diagnostic boundaries and instead focuses on clinical syndromes (49). However, for example, Hawton et al. found that depression, in particular, was a consistent predictor of repetition (27), indicating the importance of appreciating stress–diathesis models within the context of potential particular psychiatric diagnoses (as potential and common stressors), both in terms of risk prediction and also for future management planning.

Current Evidence for Neurocognition in Self-Harm

Although self-harm behavior includes much heterogeneity, the underlying demographic, clinical, and neurobiological factors are likely to be similar across individuals (47). There are putative genetic and molecular markers for self-harm behavior involving abnormalities at the neurochemical and cellular level (47). There has also been exploration into regional brain structural abnormalities in patients who have a history of self-harm and deficits of the associated brain functions (known as neurocognitive correlates) (18, 21). These neurocognitive factors may act as objective markers of self-harming behavior, overcoming self-reporting biases (47, 50). Therefore, neuroimaging studies in self-harm have a vital role, allowing us to connect structural brain abnormalities with functional and cognitive changes, and thereby produce a connected neurobiological theory to suicidal behavior.

van Heeringen and colleagues have conducted several reviews of neuroimaging studies investigating self-harm behavior (21, 47, 51). Their most recent systematic review and meta-analysis of structural and functional MRI studies examined general suicidal behavior in those with a mental illness only (21). They identified activation foci from 12 studies including 475 participants for meta-analysis (213 suicide attempters with mental illness, 262 psychiatric controls), six of which examined structural findings only, and six functional findings only. A separate narrative review identified 21 studies of structural MRI and 9 studies of functional MRI performed in those with previous suicide attempts (47). Blumberg and colleagues also published a recent review into neurobiological risk factors identified for suicidal behavior using any form of neuroimaging (52), but again their review was limited to those studies involving suicidal behavior in the context of an underlying mental illness.

These reviews indicate that specific structural findings are associated with self-harm behavior, such as reduced gray matter in the orbitofrontal cortex (OFC), the dorsolateral pre-frontal cortex (DLPFC), the anterior cingulate cortex (ACC), the insula and superior temporal gyrus, and basal ganglia, and increased volume of the amygdala (21, 47, 51, 52). There is also evidence of white-matter hyperintensities, and increased inferior frontal white-matter tracks bilaterally (such as the uncinated fasciculus and the inferior orbital fasciculus), indicating deficits in the connections between these structural areas (47, 52). Diffusion tensor imaging (DTI) studies also support anterior white-matter abnormalities and suicidal behavior (52), with identified abnormalities in frontal cortex and basal ganglia white-matter connections. These structural and connective abnormalities point to potentially impaired functioning of the amygdala–orbitofrontal–cingulate network (53), which prevents the amygdala from inhibiting the OFC and PFC, and the OFC from inhibiting the ACC appropriately. Genetic factors may be involved in these changes in basic brain structure and circuitry. For example, pre-frontal and other brain volume abnormalities are seen in first-degree relatives of those with a history of suicidal behavior, as well as in the individuals themselves (54, 55).

Functional neuroimaging studies [fMRI, single photon emission computerized tomography (SPECT), positron emission tomography (PET)] and off-line neuropsychological studies detailed and referred to in these reviews and elsewhere have been used to investigate the neurocognitive correlates of these brain regions linked to self-harm.

(i) *Decision-making:* activation of the ACC, a key player in effort-based decision-making (56), is different in young people with a previous self-harm and depression compared to those with depression but no self-harm (57). Involvement of the ACC in the process of self-harm may also explain findings of poorer Stroop performances off-line and during imaging studies in those with previous self-harm (18, 21). The OFC also appears to be related to self-harm and to decision-making. However, involvement of the OFC may relate to decisions determining reward expectation and delay (58), including "risky decision-making." Off-line, risky decision-making has been found in euthymic patients with suicidal behavior as well as healthy biological relatives of suicide completers, suggesting that it is an endophenotype with trait-like characteristics (46, 59, 60).

(ii) *Emotional-processing:* impaired processing of emotional feedback appears to be associated with self-harm behavior in both adults and adolescents in fMRI studies (61, 62). Aberrations in serotoninergic activity due to poor functioning of the PFC appear in patients with previous self-harm behavior (52), resulting in multiple deficits, including the ability to process emotional stimuli in a controlled manner (47). Furthermore, carriers of a particular (S) allele of the serotonin transporter gene, 5HTTLPR, appear to have reduced functional connectivity between the ACC and amygdala (63, 64). Thereby, emotional-processing and self-harm appear to be connected in terms of genetic, structural, connective, and functional studies.

(iii) *Memory:* impairments in memory also seem to be present in patients with self-harm with and without mood disorder (65), although there is little in terms of neuroimaging evidence. Off-line, working memory and executive function deficits (for example, on the Iowa gambling task and verbal

fluency) in particular are associated with self-harm in the context of mood disorders (18). A recent systematic review of studies in psychiatric patients found that autobiographical memory was significantly less specific and more general in patients with a previous suicide attempt relative to those without, and long-term and working memory were both more impaired in suicide attempters than in patient and healthy controls (66).

In their recent synthesis and meta-analysis of the fMRI data relating to neurocognition and self-harm in mental illness (21), van Heeringen and colleagues found a cluster in the dorsal ACC showing increased activation in suicide attempters when compared to psychiatric controls during exposure to angry faces or mildly happy faces, while activation was reduced in suicide attempters versus psychiatric controls for high-risk decisions. Similarly, a cluster in the rostral ACC showed increased activation in suicide attempters compared to psychiatric controls during exposure to angry faces while activation was reduced in attempters compared to controls during Go/No-Go tasks. Therefore, synthesis of evidence from off-line studies, and structural and functional imaging, indicates the following hypothesis of neurocognition in self-harm: in those with self-harm, there appears to be increased activation during emotional tasks (such as exposure to emotionally charged faces) in the ACC, and decreased activation during non-emotional cognitive tasks (such as decision-making) in the ACC (21). In van Heeringen's review, there were no studies found directly linking structural and functional changes in the brain in the context of self-harm (21). However, he suggests that his functional meta-analysis may be put in the context of the known structural deficits previously described above (21). In other words, an underactive pre-frontal cortex is unable to respond appropriately to non-emotional stimuli, or inhibit a hyperactive emotionally-/threat-driven limbic system.

Current Evidence for Neurocognition in Repetition of Self-Harm, and Its Use in Prediction

Repetition of self-harm with an increasing risk of suicide can be understood as an "escalating disinhibition syndrome." Therefore, studies examining repetition and facets of executive control (67) are likely to be very important, such as response inhibition, interference, attention, decision-making, and cognitive flexibility.

However, there is almost no imaging data examining repetition of self-harm. We recently conducted a systematic review (de Cates et al., in preparation) into repetition of self-harm and neurocognition, which indicated that there is only one published conference abstract of an imaging study examining emotional-processing (68). In terms of off-line studies, only a very few studies have examined decision-making (69–71), although each of these demonstrated evidence of an association between impaired decision-making and increased risk of repetition. There were also associations for repetition of self-harm with specific attentional biases on a modified emotional-Stroop test (72); specific results on the test predicted future self-harm better than underlying mood disorder or clinician ratings. Cognitive inflexibility predicted future suicidal ideation in those with a past history of self-harm (73). Rasmussen and colleagues found an association between recall of positive autobiographical memories, but not negative memories, and repetition of self-harm in an exploratory study (74). These studies indicate that poor functioning or impairments in terms of neurocognition may be associated with increased risk of repetition. However, it is less clear if we can apply these correlates clinically: that is, use assessment of these factors in an individual to predict the risk of future self-harm. This personalized neurocognitive profile might also provide potential targets for therapeutic interventions aimed at reducing this risk.

HOW COULD NEUROCOGNITION BE USED TO GUIDE TREATMENT FOR REPETITION OF SELF-HARM?

Extrapolating from the non-repetition data, there may be several potential neurocognitive avenues to identify risk of repeating self-harm, and potential modes of intervention. Psychotherapy techniques may be helpful, such as cognitive therapy or training (75, 76), or dialectical behavioral therapy in situations such as personality disorder (77). However, there have been few replications of psychological therapies for self-harm (19) and no specific work in multiple attempters. For adolescents with multiple episodes of self-harm, mentalization therapy (based on understanding actions in terms of thoughts and feelings) (78) shows promise at reducing repetition frequency (79), but the effect was modest and the one trial was small (80). Non-invasive neurophysiological techniques, such as repetitive transcranial magnetic stimulation (rTMS), may prove to be effective (81–83). For example, we can increase risky decision-making in men by inhibiting cortical function with TMS (84). Therefore, may it be possible to improve cognition and ineffective decision-making by a similar method, for example, as van Heeringen suggests, by directing rTMS at the DLPFC to modify function in the OFC and hopefully reduce risky decisions (47)?

Previous investigations into potential medical treatments for self-harm have included antidepressants, mood stabilizers, and natural products, but no significant treatment effect on repetition of self-harm was found for any of these options in a recent Cochrane review, although the quality of evidence was low (85). Only one antipsychotic, Flupenthixol showed promise, but again the quality of the evidence was very low. However, perhaps we are not examining the correct potential medication in the correct circumstance. We know that emotional processing, in particular, is controlled by serotonin, and relates to amygdala functioning. However, amygdala responses to fearful faces are modified by antidepressant use in depressed patients (86, 87). If we could identify a group of individuals with self-harm behavior and emotional-processing deficiencies, might they receive a particular benefit from antidepressants? A large body of evidence indicates that Lithium and Clozapine are anti-suicidal unrelated to their efficacy as a mood stabilizer and antipsychotic, respectively, possibly related to their serotoninergic effects (88, 89), as well as Lithium's effect of reducing cell death and potentially increasing brain volume (90). However, as yet, there has been

little or no practice of using Lithium or Clozapine as a prevention strategy outside of mood disorder (or violent behavior), or psychotic disorder, respectively. These may also be an avenue for further exploration. Furthermore, could we consider existing pharmacological regimes than have evidence for promoting non-emotional neurocognition and memory in other disorders, such as acetylcholinesterase inhibitors typically used for Alzheimer's dementia? Another possibility for further research is ketamine, an NMDA antagonist that is finding increasing support for its use as an antidepressant (91). Rapid suppression of suicidal ideation has also been noticed in depressed patients treated with ketamine (92), making it a potential treatment for high-risk suicidal ideation to prevent imminent self-harm (93). However, the specific brain regions involved in ketamine's ability to reduce suicidal ideation are unknown and much further work is required, including animal studies or similar before it can be considered for clinical trials.

Therefore, the dearth of imaging studies examining repetition in particular is concerning considering the individual, financial, and social implications of people who repeat self-harm frequently and/or die by suicide. Until we investigate the functional neurocognitive basis underlying repetition of self-harm in a basic-science (i.e., brain regions and networks) and systematic manner using second-generational imaging techniques, we will be unable to inform third-generational imaging and potential future clinical applications, of which there may be many. Potentially combining research into imaging and genetics may yield fruit, particularly in terms of neurochemistry alleles. However, clearing several process issues may help, such as reaching a consensus in terms of phenomenology of self-harm and associated thoughts and behaviors.

AUTHOR CONTRIBUTIONS

Both authors devised the article topic. Both authors contributed to the original research detailed in the article. AdeC drafted the article and both authors revised the article.

FUNDING

AdeC is funded by an NIHR (National Institute of Health Research) Academic Clinical Fellowship. The NIHR played no other role in the research discussed in this manuscript.

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Conflict of Interest Statement: Both the authors declare that the research discussed in this manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 15 April 2016
doi: 10.3389/fpsyt.2016.00062

Bilingualism as a Contributor to Cognitive Reserve? Evidence from Cerebral Glucose Metabolism in Mild Cognitive Impairment and Alzheimer's Disease

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Objective: Bilingualism is discussed as one factor contributing to "cognitive reserve" (CR), as it enhances executive control functions. To elucidate the underlying cerebral correlates, regional glucose uptake was compared between bilinguals and monolinguals with mild cognitive impairment (MCI) and beginning-stage Alzheimer's disease (AD) by using [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET).

Methods: Thirty patients (73.2 ± 7.4) diagnosed with MCI or probable AD received physical and neuropsychological examinations, blood tests, and FDG-PET scans. Sixteen patients were classified as lifelong bilinguals, following the criterion of Bialystok et al., and groups were matched for age, sex, and mini mental state examination scores. Analyses were conducted using statistical parametric mapping version 8. The whole brain was used as reference region for intensity normalization and years of education were controlled for.

Results: Bilingual patient groups showed substantially greater impairment of glucose uptake in frontotemporal and parietal regions [including Brodmann areas (BAs) 9, 47, 40, and 21] and in the left cerebellum relative to monolingual patients.

Conclusion: Bilingualism is likely to contribute to CR, given that bilingual patients showed more severe brain changes than monolinguals when adjusting for severity of cognitive impairment. The latter did not only comprise BAs relevant to speech and language but also structures typically involved in AD pathology, such as the temporal and the parietal cortices.

Keywords: bilingualism, cognitive reserve, Alzheimer's disease, mild cognitive impairment, FDG-PET

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Ellen Bialystok, York University, Canada
Thomas Leyhe, Universitäre Psychiatrische Kliniken Basel, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *28 January 2016*
Accepted: *29 March 2016*
Published: *15 April 2016*

Citation:
Kowoll ME, Degen C, Gorenc L, Küntzelmann A, Fellhauer I, Giesel F, Haberkorn U and Schröder J (2016) Bilingualism as a Contributor to Cognitive Reserve? Evidence from Cerebral Glucose Metabolism in Mild Cognitive Impairment and Alzheimer's Disease. Front. Psychiatry 7:62. doi: 10.3389/fpsyt.2016.00062

INTRODUCTION

Lifelong bilingualism is associated with higher cognitive reserve (CR), as it is linked to relatively delayed onset of Alzheimer's disease (AD)-related cognitive deficits (1–4) and the manifestation of mild cognitive impairment (MCI) and AD (4–6). CR facilitates compensation of pathological cerebral changes for a longer period of time; hence, in neuroimaging studies, patients with higher

CR typically show more pronounced changes than those with a low CR despite similar levels of impairment. The only study to test this effect in bilinguals was presented by Schweizer et al. (7), who compared indices of brain atrophy using computed tomography (CT) scans of 20 monolingual and 20 bilingual patients diagnosed with probable AD, carefully matched for level of cognitive performance and years of education. Bilingual patients with AD exhibited substantially more pronounced brain atrophy than monolingual patients in indices sensitive to mid temporal changes, specifically the radial width of the temporal horn and the temporal horn ratio.

In the present study, we sought to investigate differences in cerebral glucose metabolism between bilinguals and monolinguals with MCI and AD using [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) under a resting condition, i.e., a neuroimaging technique particularly sensitive to detect AD-related brain changes. We expected to find a substantially greater impairment of glucose uptake in bilinguals than monolinguals.

MATERIALS AND METHODS

Participants

A total of 30 subjects were recruited between June 2012 and March 2014 from the Memory Clinic of the University of Heidelberg. Fourteen subjects were classified as monolinguals, 16 as lifelong bilinguals, following Bialystok et al.'s [p. 460, Ref. (1)] criterion: patients were classified as bilingual if they "… had spent the majority of their lives, at least from early adulthood, regularly using at least two languages," 12 were diagnosed with MCI, according to the aging-associated cognitive decline criteria [AACD; (8)], and 18 individuals were diagnosed with AD, using the NINCDS–ADRDA criteria (9). Diagnoses were established by consensus between an experienced geriatric psychiatrist and an experienced psychologist.

The bilingual participants consisted of speakers of nine different first languages, of which the most common were German ($N = 7$) and Hungarian ($N = 2$). There were seven different second languages spoken, the most common were German ($N = 8$) and English ($N = 3$). Also, 68.8% ($N = 11$) of bilinguals were multilinguals and were able to use more than two languages. Twelve bilinguals were immigrants to Germany. Their countries of origin were Hungary ($N = 2$), Czechoslovakia, Finland, Palestine, Poland, Peru, Serbia, Slovakia, Taiwan, Trinidad, and Turkey (each $N = 1$).

Procedure

The study was approved by the Ethical Committee of the University of Heidelberg. After complete description of the study to the participants, informed consent was obtained. Participants were carefully screened for language history, occupational history, fluency in German and other languages, place of birth, and date of immigration.

Neuropsychological Test Battery

Neuropsychological assessment contained the German version of the CERAD-NP neuropsychological assessment battery (10, 11), the mini-mental state examination (MMSE), the Trail Making Test (TMT) (12), the subtests logical memory and digit span of the German version of Wechsler Memory Scale (WMS-R and WMS-IV) (13, 14), and the clock-drawing test (15). Furthermore, the short version of the Geriatric Depression Scale (GDS) (16) was obtained to exclude depressive symptoms. On the basis of interviews and tests, severity of dementia was rated by using the Global Deterioration Scale (17).

PET Acquisition Protocol

Following a 6-h fasting, blood glucose level was determined and shown to be below 110 mg/dl in all subjects, before the injection of 118–196 MBq FDG. From 15 min before until 45 min after injection, participants rested in a quiet room with dimmed light. They were instructed to keep their eyes closed. Afterward, 20-min PET scans were acquired. Measurements were obtained with a Biograph 6 by Siemens (thickness of each slice: 5 mm, kVp: 130, pixel size: 0.59 mm × 0.59 mm, and matrix: 512 × 512) [for details, see Ref. (18, 19)].

Image Analysis

Statistical parametric mapping version 8 (SPM8) routines with default settings were used for basic image processing.[1] Global normalization was conducted using the proportional scaling option as provided by SPM8. Images were spatially normalized to the Montreal Neurological Institute PET template, written on a matrix with 2 mm × 2 mm × 2 mm voxel size, and smoothed by an isotropic Gaussian filter of 12 mm full width at half maximum [for details, see Ref. (19)].

Statistical Analyses

For statistical analyses, raw data from the individual CERAD, WMS, and TMT subscores were transformed into *z*-scores that were adjusted for age, gender, and years of education (11–14).

For voxel-based parametric analysis with SPM8, years of education were entered as a covariate. The predicted value was the global normalized glucose uptake. Assuming independency and normal distribution of error terms and homoscedasticity, we performed pairwise one-sided *t*-contrasts for the effect of language group using the contrast matrix (−1, 1) (bilingual < monolingual). Significance level was set to $p < 0.05$ (uncorrected) with cluster extent threshold $k > 30$. The respective structures were identified by their coordinates, according to the Talairach atlas (20) using the Talairach client applet version 2.4.2.[2] SPSS for Windows version 22 was used for statistical analyses; $p < 0.05$ was considered significant. Likelihood-ratio tests were used where appropriate [for details, see Ref. (19)].

RESULTS

Demographic and clinical characteristics of the language groups and the total sample are provided in **Table 1**.

Bilinguals have had more years of education than monolinguals. Moreover, bilinguals were more likely to be immigrants

[1] http://www.fil.ion.ucl.ac.uk/spm/software/spm8/
[2] http://www.talairach.org/index.html

TABLE 1 | Demographic and clinical characteristics of bilingual and monolingual patients with MCI and AD.

M ± SD/*N*	Total sample	Bilinguals with MCI and AD (A)	Monolinguals with MCI and AD (B)	*t*-Test/likelihood ratio	
N	30	16	14		
Age	73.2 (7.4)	74.6 (6.8)	71.6 (7.9)	$t(28) = 1.109$ $p = 0.277$	
♂/♀	14/16	8/8	6/8	LR(1) = 0.153 $p = 0.695$	
MMSE	24.4 (2.9)	24.9 (2.7)	23.9 (3.1)	$t(28) = 0.955$ $p = 0.348$	
Born in Germany/immigrant to Germany	16/14	4/12	12/2	LR(1) = 11.977*** $p = 0.001$	
Years of education	13.6 (4.0)	15.3 (3.6)	11.7 (3.7)	$t(28) = 2.644$* $p = 0.013$	A > B
MCI/AD	12/18	5/11	7/7	LR(3) = 41.455*** $p = 0.000$	
Geriatric Depression Scale	2.7 (3.3)	2.7 (3.1)	2.6 (3.7)	$t(26) = 0.091$ $p = 0.928$	
Global Deterioration Scale	3.2 (0.7)	3.1 (0.8)	3.4 (0.5)	$t(28) = -0.932$ $p = 0.359$	
Clock-drawing test	2.2 (1.1)	2.1 (1.2)	2.4 (1.1)	$t(28) = -0.552$ $p = 0.585$	

LR, likelihood quotient.
*$p < 0.05$.
***$p \leq 0.001$.

than monolinguals and exhibited a higher proportion of AD pathology as opposed to MCI. Scores on the GDS, the Global Deterioration Scale, and the MMSE showed only minor, non-significant differences between groups (**Table 1**).

Neuropsychological performance was compared between language groups (**Table 2**). Overall performance was affected equally in monolinguals and bilinguals. No significant differences occurred.

Significant differences in FDG uptake were restricted to lower values in the bilingual vs. monolingual comparison and involved both right and left frontal, temporal and parietal cortices, and the left cerebellum (**Figure 1**).

As given in **Table 3**, these regions included Brodmann area (BA) 9, 21, 40, and 47.

DISCUSSION

The present study yielded significantly lower glucose uptake in bilingual compared to monolingual patients with MCI or early AD, although both groups were comparable on clinical grounds. Differences in glucose uptake were localized in areas important for speech and language, mainly involving the frontal cortices as well as in temporoparietal areas traditionally associated with AD pathology (21) and in the left cerebellum. These regions included BA 9 (right), 21 (right), 40 (right and left), and 47 (left). There were no significant differences in neuropsychological domains between monolinguals and bilinguals. These results are in line with the results of Kowoll et al. (22), who showed that bilingual MCI and AD patients showed a similar pattern of neuropsychological deficits as monolingual patients did. This finding also included the TMT-B, which addresses aspects of frontal executive functioning – a domain which seems to be enhanced in healthy bilinguals [(23–25); reviewed in Ref. (26)]. The performance in the BNT – a test in which healthy monolingual subjects usually achieve better scores [(24, 27); reviewed in Ref. (28)] was equally affected in the two language groups in this analysis. Since groups showed only minor, non-significant differences with respect to severity of cognitive deficits, these findings corroborate the hypothesis that bilingualism facilitates compensation of cerebral changes and can thus contribute to CR. That bilinguals also show differences in centers responsible for speech and language processing seems plausible, given the fact that patients differed with respect to language (monolinguals vs. bilinguals) while displaying similar degrees of cognitive impairment.

Brodmann area 9 in the right hemisphere is located in the frontal cortex and contributes to dorsolateral and medial prefrontal cortex functions linked to working memory (29), visuospatial memory (30), and planning (31). BA 21 is located in the middle temporal gyrus, which is involved in language and semantic memory processing (32–35). Likewise, Schröder et al. (21) found BA 21 (both right and left) to be involved in a declarative memory task, using FDG-PET. BA 40 includes Wernicke's area of the supramarginal gyrus and is functionally involved in reading, meaning, and phonology (36). BA 47 has been implicated in the processing of fine structured stimuli that evolve over time, not merely those that are linguistic (37). Moreover, Dos Santos et al. (38) analyzed neuropsychological deficits with respect to morphometric changes in 94 patients with MCI and AD and found deficits in verbal fluency and word recognition to be significantly correlated with changes in the left gyrus frontalis inferior (BA 47).

Our findings parallel the results reported by Gold et al. (39), who provided the first direct evidence of a neural basis for

TABLE 2 | *z*-Scores (means) for the subscales "logical memory" and "digit span" of the Wechsler Memory Scale and TMT and the subscales of CERAD-NP in bilinguals and monolinguals with MCI and AD.

M ± SD/*N*	Total sample	Bilinguals with MCI and AD (A)	Monolinguals with MCI and AD (B)	*t*-Test
N	30	16	14	
Word list immediate recall	−2.2 (1.2)	−2.0 (1.4)	−2.3 (0.8)	$t(25) = 0.595$ $p = 0.557$
Word list delayed recall	−1.8 (1.2)	−1.5 (1.3)	−2.2 (1.0)	$t(25) = 1.534$ $p = 0.138$
Word list recognition	−1.5 (2.3)	−1.5 (2.7)	−1.5 (1.6)	$t(25) = -0.059$ $p = 0.954$
Constructional praxis	−0.3 (1.6)	−0.1 (1.3)	−0.6 (2.0)	$t(27) = 0.848$ $p = 0.404$
Constructional praxis recall	−2.1 (1.7)	−2.1 (1.9)	−2.0 (1.3)	$t(27) = -0.139$ $p = 0.890$
Verbal fluency	−1.3 (1.0)	−1.4 (0.8)	−1.2 (1.3)	$t(28) = -0.515$ $p = 0.611$
BNT	−0.8 (1.7)	−0.4 (1.4)	−1.2 (1.9)	$t(28) = 1.446$ $p = 0.159$
TMT-A	−3.3 (4.6)	−3.7 (5.4)	−2.7 (3.7)	$t(28) = -0.560$ $p = 0.580$
TMT-B	−4.2 (6.4)	−4.0 (7.4)	−4.5 (5.3)	$t(20) = 0.190$ $p = 0.851$
Logical memory I	−2.1 (1.1)	−2.0 (1.2)	−2.1 (1.1)	$t(26) = 0.279$ $p = 0.782$
Logical memory II	−2.5 (1.0)	−2.3 (1.0)	−2.7 (0.9)	$t(26) = 1.015$ $p = 0.320$
Digit span forward	−1.0 (1.0)	−1.0 (1.2)	−1.1 (0.8)	$t(28) = 0.255$ $p = 0.801$
Digit span backward	−0.9 (1.0)	−0.9 (0.9)	−0.9 (1.0)	$t(28) = -0.111$ $p = 0.912$

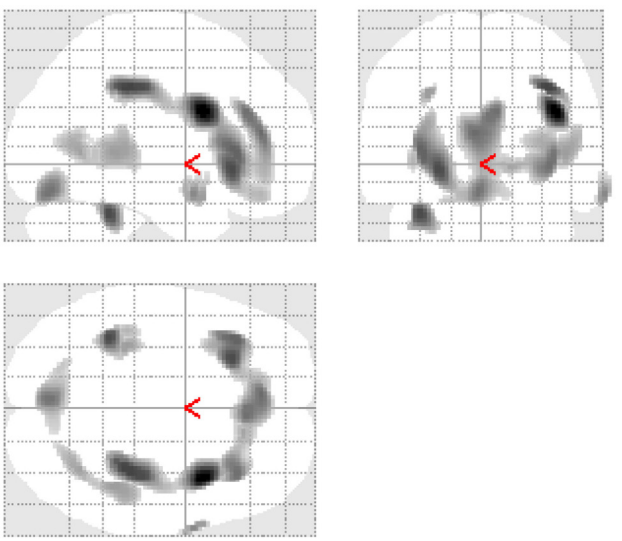

FIGURE 1 | Glass brains demonstrating significant reduction of glucose metabolism between groups.

bilingual cognitive control advantages in aging. The authors compared the reaction times of 80 younger and older adult monolinguals and bilinguals who completed the same perceptual

TABLE 3 | Reduced glucose metabolism in bilingual MCI and AD patients vs. monolingual MCI and AD patients.

	Location	BA	Cluster extension	Peak *z*-value	*p*	*x*	*y*	*z*
R	**Gyrus frontalis inferior**	**9**	**3357**	**2.56**	**0.005**	**40**	**8**	**26**
R	Inferior parietal lobe	40		2.28	0.011	36	−32	38
L	Gyrus frontalis inferior	47		2.25	0.012	−26	24	−6
L	**Cerebellum, culmen**	–	**207**	**2.25**	**0.012**	**−36**	**−44**	**−30**
L	**Cerebellum**	–	**441**	**2.08**	**0.019**	**−4**	**−78**	**−18**
L	Cerebellum, declive	–		1.76	0.039	−20	−72	−22
R	**Gyrus temporalis medius**	**21**	**51**	**2.00**	**0.023**	**66**	**2**	**−18**
L	**Inferior parietal lobe**	**40**	**40**	**1.93**	**0.027**	**−32**	**−34**	**34**
		–	**472**	**1.92**	**0.027**	**44**	**−40**	**4**
		–		1.90	0.029	34	−60	4
		–		1.78	0.037	42	−52	2
L	**Temporal lobe, sub-gyral**	–	**89**	**1.83**	**0.034**	**−40**	**−34**	**0**

R, right; L, left; BA, Brodmann area.

Cluster extension represents the number of contiguous voxel passing the threshold of $p < 0.05$. Bold markings delineate a cluster and the peak z-value. Brain regions are indicated by Talairach and Tournoux coordinates, x, y, and z: x: the medial to lateral distance relative to the midline (positive: right hemisphere), y: the anterior to posterior distance relative to the anterior commissure (positive: anterior), and z: the superior to inferior distance relative to the anterior commissure–posterior commissure line (positive: superior) [for details, see Ref. (18)].

task-switching experiment while functional magnetic resonance imaging (fMRI) was conducted. The researchers observed that bilingual older adults outperformed their monolingual peers with decreased signaling in left lateral frontal and cingulate cortices. This activation increases were directly correlated with enhanced performance on the task-switching task.

Corroborating results of Schweizer et al. (7), our FDG-PET study shows that a group of bilingual patients with AD exhibit substantially greater amounts of brain pathology than monolingual patients when the two groups were matched for level of severity of impairment. Differences in years of education between the two groups were statistically controlled for.

The respective brain regions identified in our study are not only associated with speech and language but also implicated in a number of cognitive functions typically compromised in AD. These findings indicate that bilinguals can compensate for more severe cerebral changes than monolingual patients in the early phases of AD.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

The study was supported by the "Ministry for Work, Social Order, Family, Women and Senior Citizen" of the State Baden-Württemberg, Germany, and the "Robert Bosch Foundation/ Stuttgart," Germany.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 26 February 2016
doi: 10.3389/fpsyt.2016.00022

15 Years of Microstate Research in Schizophrenia – Where Are We? A Meta-Analysis

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Schizophrenia patients show abnormalities in a broad range of task demands. Therefore, an explanation common to all these abnormalities has to be sought independently of any particular task, ideally in the brain dynamics before a task takes place or during resting state. For the neurobiological investigation of such baseline states, EEG microstate analysis is particularly well suited, because it identifies subsecond global states of stable connectivity patterns directly related to the recruitment of different types of information processing modes (e.g., integration of top-down and bottom-up information). Meanwhile, there is an accumulation of evidence that particular microstate networks are selectively affected in schizophrenia. To obtain an overall estimate of the effect size of these microstate abnormalities, we present a systematic meta-analysis over all studies available to date relating EEG microstates to schizophrenia. Results showed medium size effects for two classes of microstates, namely, a class labeled C that was found to be more frequent in schizophrenia and a class labeled D that was found to be shortened. These abnormalities may correspond to core symptoms of schizophrenia, e.g., insufficient reality testing and self-monitoring as during auditory verbal hallucinations. As interventional studies have shown that these microstate features may be systematically affected using antipsychotic drugs or neurofeedback interventions, these findings may help introducing novel diagnostic and treatment options.

Keywords: microstates, schizophrenia, EEG, neurofeedback, saliency

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Christoph Mulert, Universitätsklinikum Hamburg-Eppendorf, Germany
Avinash Ramyead, University of Basel Psychiatric Clinics, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *04 December 2015*
Accepted: *09 February 2016*
Published: *26 February 2016*

Citation:
Rieger K, Diaz Hernandez L, Baenninger A and Koenig T (2016) 15 Years of Microstate Research in Schizophrenia – Where Are We? A Meta-Analysis. Front. Psychiatry 7:22. doi: 10.3389/fpsyt.2016.00022

INTRODUCTION

Schizophrenia is a psychiatric disorder showing a broad range of deficits across a multitude of task demands (1). Therefore, an explanation common to all these abnormalities has to be sought independently of any particular task but instead during baseline states, i.e., before a task takes place or during rest. In addition, and under the scope of the "disconnection hypothesis" of schizophrenia (2), it does not seem reasonable to assume that an isolated local system can account for these deficits, but rather, a dysfunctional integration among neural systems. Research on the neurobiology of schizophrenia accumulates a large body of evidence supporting this approach (3–5). Relevant findings among others include abnormal pruning of connections during adolescence (6), structural abnormalities in white matter tracks (7, 8) and alterations of brain functional connectivity during task execution as well as during rest (9, 10).

EEG research has long reported abnormalities in schizophrenia patients [see Ref. (11) for an overview] and has provided substantial support to the disconnection hypothesis (12–14). Importantly, evidence for abnormal dynamics of particular transiently stable functional brain networks has repeatedly been reported in relation to schizophrenia. The aforementioned functional networks were identified using EEG microstate analysis (15, 16) and are the so-called EEG resting-state networks (15–18). For a comprehensive outlook on microstates, we refer the reader to the recent review by Khanna et al. (18).

Microstate analysis of the ongoing EEG shows subsecond periods of quasi-stable spatial configurations that have been linked to fMRI resting-state networks (19). The fact that the simultaneity of events across distributed regions is a defining property of microstates coincides well with theoretical considerations about the role of synchronization for the integration of brain activity into something that is subjectively experienced as unitary (20). The sequence of microstates and the rules potentially governing these sequences [the so-called microstate syntax (21)] may represent the subsecond switching between various types of such integrative states (18).

Interestingly, the observed microstate configurations repeat within and across subjects. This allows the investigation of a limited set of prototypical microstate configurations using spatial clustering algorithms (16, 22). These prototypical configurations can then be used to efficiently quantify multi-subject EEG resting-state data. Over the past 15 years, ongoing research has been able to systematically link changes in EEG microstate quantifiers in domains, such as schizophrenia research (13, 21, 23–28), development (29), perceptual modes (30), and fMRI resting-state networks (19) or sleep (31).

In this paper, we present the results of a meta-analysis on all publications that so far have bound together schizophrenia and microstates. As interventional studies have shown that these microstate features may be systematically affected using conventional [i.e., medication as in (13)] or neurofeedback (NFB) interventions (32), the findings may help boosting the development of novel diagnostic and treatment options.

MATERIALS AND METHODS

To identify the relevant literature, we conducted a PubMed search with the terms "schizophrenia" and "microstate." The resulting papers were then reviewed for particular criteria chosen to assure a sufficient comparability of the extracted microstate parameters across studies. These criteria were the following: (1) the paper reported original findings, (2) the electrode array used for the analysis covered at least the area of the standard 10-20 system, (3) four microstate classes were fitted to the data (being the most frequently used number of microstate classes across studies), and (4) subjects were recorded in a task-free resting-state condition. Care was taken to exclude the duplicate reporting of data in different papers. Note that the justification of the choice of these criteria was purely pragmatic; it identified the broadest common ground to compare studies on microstates in schizophrenia at the time of this paper being written. We do not imply that these criteria are the optimal choice to investigate microstates in general. In addition of the papers identified by the PubMed search, we were aware of, and included one more study that met the above criteria and had been accepted for publication, but was not yet registered in PubMed (28). The employed search and selection criteria are shown in **Figure 1**. A complete list of all papers found in PubMed with a brief rationale for inclusion/exclusion is given in Table S1 in Supplementary Material.

There was a total of seven studies meeting our criteria, beginning with a paper in 1999 (23) and ending with the most recent paper by Tomescu et al. (28). The included papers are shown in **Table 1**, together with the central characteristics of the studied population. Note, however, that the multicenter-study by Lehmann et al. (21) included a small (six patients and six controls) subset of subjects where the midline electrodes were interpolated. Since the data were only presented across all study centers and since there were many more subjects from other centers, we decided to include this study despite this fact.

Importantly, all of these studies were based on a topographically consistent set of four prototypical microstate classes that were labeled from A to D according to the similarity of the obtained microstate classes with the microstate prototype maps reported in the first study of this kind (23). In addition, these papers were coherent and largely complete in the microstate parameters they reported, namely, coverage (percent total analysis time covered by each microstate class), occurrence (number of microstates observed per second for each microstate class), and mean duration (average duration of microstates of a given class). From all of these studies, mean and standard deviation (SD) of patient and control data were available for most of the typical microstate parameters and thus collected for the meta-analysis. Where data before and after medication were available, the data obtained before medication were used. An overview of the methodological content of the included studies is illustrated in **Table 1**.

The means and SDs of each study were used to compute hedges-g and its SD as standardized measure of within-study effect size. This computation was conducted using the package "compute.es" (34) of the R-software (35). The obtained within-study effect sizes were then weighted by their inverse variance to

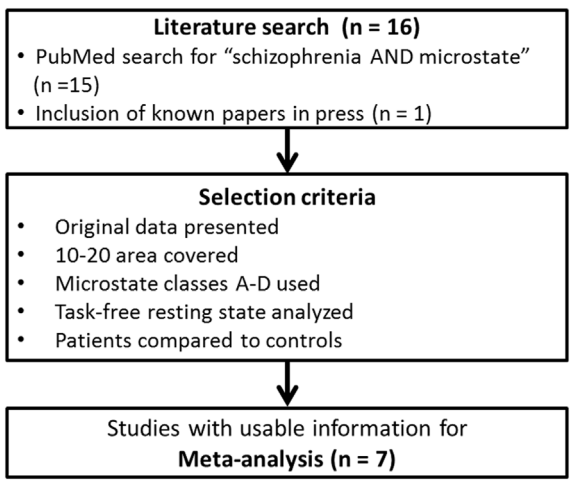

FIGURE 1 | Selection process of the included studies in the meta-analysis.

TABLE 1 | Studies included.

Reference	*n*	Diagnosis	Comorbidity included	Medication	Age	Gender		Channels	Recruitment area
						M	F		
Koenig et al. (23)	9	DSM-IV: 295.30 paranoid type DSM-IV: 295.40 schizophrenieform dis.	n.a.[a]	No	24.82 (range: ± 6.67)	3	6	19	Switzerland
Lehmann et al. (21)	27	DSM-IV: 295.30 paranoid type DSM-IV: 295.90 undifferentiated type DSM-IV: 295.10 hebephrenic type DSM-IV: 295.20 catatonic type	n.a.[a]	No	23.9 (SD: 4.5)	18	9	16–21[b]	Japan, Italy, and Germany
Kikuchi et al. (13)	21	DSM-IV: 295.30 paranoid type DSM-IV: 295.10 disorganized type	n.a.	No	28.1	11	10	18	Japan
Nishida et al. (33)	18	DSM-IV: 295[c]	n.a.[a]	No	24.50 (SD: 6.3)	10	10	19	Japan
Andreou et al. (26)	18	DSM-IV: 295[c]	Depressive dis. Substance related dis. Personality dis.	Yes	23.67 (SD: 4.4)	16	2	64	Germany
Tomescu et al. (27)	30	High risk patients	Anxiety dis. ADHD Mood dis. Schizophreniform dis.	Yes	16.5 (range: ± 2.5)	13	17	204	Switzerland
Tomescu et al. (28)	27[d]	DSM-IV: 295[c]	n.a.	Yes	34.5 (range: ± 9.5)	14	13	64	Georgia

[a]*Excluded, if it might involve or affect brain function.*
[b]*16: Italy, 19: Japan, and 21: Germany.*
[c]*No specification.*
[d]*Only part of the sample included to avoid overlapping samples.*

obtain a weighted mean effect size across studies, and the standard error of these mean effect sizes was extracted. In order to test the significance of the obtained overall mean effect sizes, a *Z*-test was conducted, and the upper and lower confidence intervals were computed. This yielded a total of 12 tests, each one assessing a potential difference between patients and controls in one of the three microstate features and in one of the four microstate classes. Since the single-subject data were not available, it was not possible to extend the analysis to a multifactorial level that would assess the overall significance of group by microstate class interactions. In order to correct for potential false positives due to multiple testing, a Bonferroni correction was applied with a factor of 8. This factor was chosen because all studies reported four microstate classes, and all studies reported two independent features (occurrence and mean duration) per microstate class. The sometimes additionally reported coverage can be computed from occurrence and mean duration and was thus not considered as an additional independent test.

Significant overall mean effects were tested for potential confounding effects of medication by excluding studies that had investigated patients under medication. The results of EEG microstate features yielding significant mean effects were displayed using forest plots.

RESULTS

The forest plots of the significant mean effect sizes are shown in **Figure 2**. The meta-analysis yielded significant mean effect sizes of medium size for microstates of class C, where a consistent increase was present and microstates of class D, where a reduction was observed. Namely, microstates of class C were found to occur more frequently in schizophrenia ($g = 0.760$, uncorrected $p = 0.0003$, and corrected $p = 0.0024$) and to cover more percent of time ($g = 0.569$, uncorrected $p = 0.011$, and corrected $p = 0.088$), whereas no significant effect was found for mean duration ($g = 0.176$ and uncorrected $p = 0.39$). Contrary to that, microstates of class D were found to cover less percent time ($g = -0.759$, uncorrected $p = 0.0008$, and corrected $p = 0.0064$) and to last shorter in the mean ($g = -0.712$, uncorrected $p = 0.0007$, and corrected $p = 0.0056$), whereas no consistent change in occurrence could be identified ($g = -0.351$ and uncorrected $p = 0.090$). When excluding studies with medicated patients, these effects were preserved and mostly showed increased effect sizes (contribution class C: $g = 0.393$, occurrence class C: $g = 0.800$, contribution class D: $g = -0.821$, and duration class D: $g = -0.970$), which makes it unlikely that these effects can be attributed to medication.

In addition, the meta-analysis showed a small, but significant, effect size for a shortening of microstate class B ($g = -0.435$ and $p = 0.037$) that also increased when only unmedicated patients were considered ($g = -0.679$ and $p = 0.017$). However, this effect was not significant after Bonferroni correction. The meta-analyses did not identify any consistent effects in microstate class A.

DISCUSSION

The present study introduces the overall evidence for alterations of EEG microstates in schizophrenia patients, based on all available

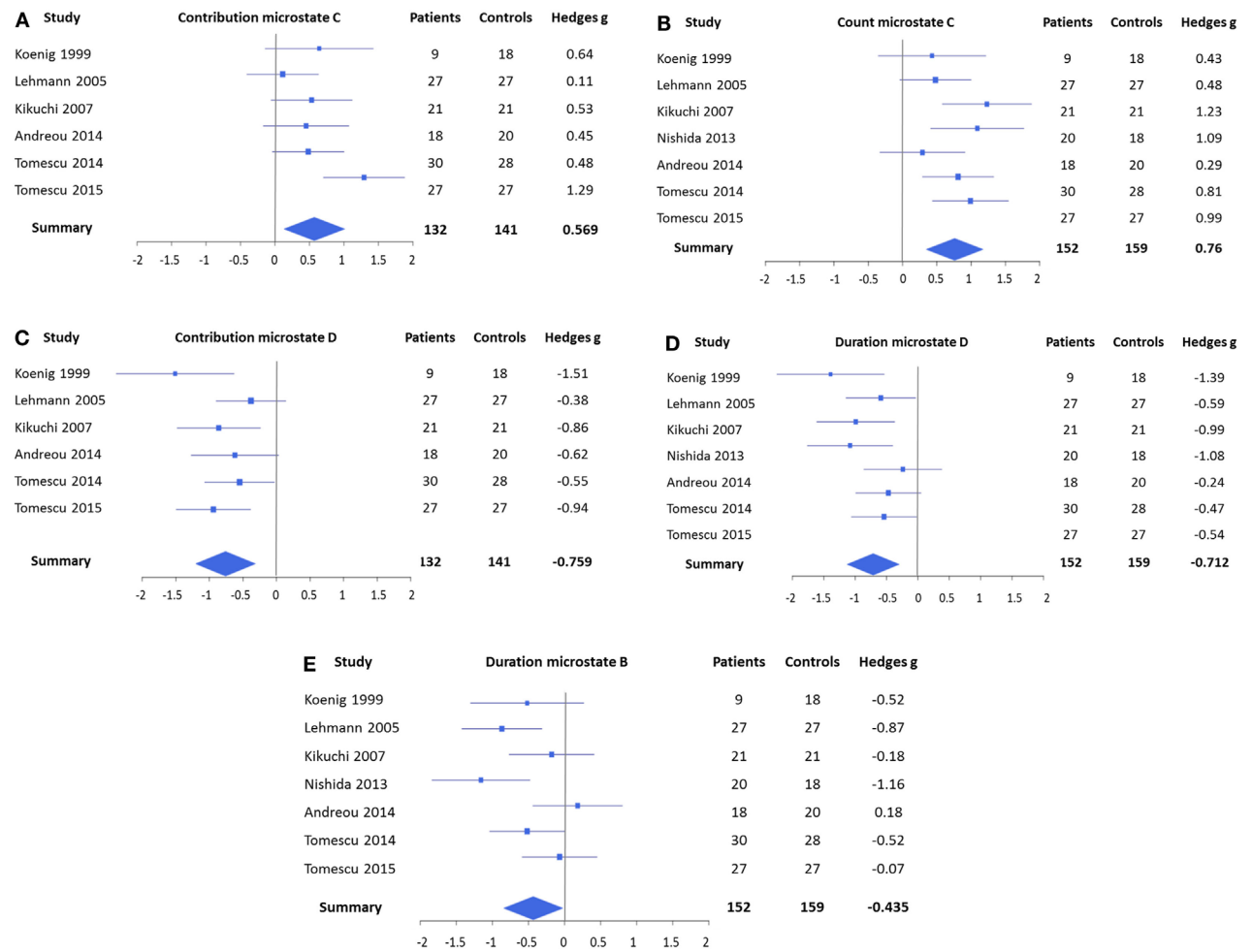

FIGURE 2 | Forest plots representing the EEG microstate features that yielded significant mean effects in the meta-analysis. **(A)** Contribution of microstates of class C, which covered more percent time in patients, and **(B)** count of microstates of class C, which occurred also more frequently. **(C)** Contribution of microstates of class D, which covered less percent of time in patients, and **(D)** duration of microstates of class D, which was found to be shorter. **(E)** Duration of microstates of class B was shorter in patients. Note that the contribution of microstates of class C **(A)** and the duration of microstates of class B **(E)** were not significant after Bonferroni correction. No significant effects were found for mean duration of microstates of class C, count of microstates of class D, and count and contribution of microstates of class B.

studies that could reasonably be included in a meta-analysis. The inclusion criteria for the studies were defined by the pragmatic objective of maximizing the amount of studies to be compared, which implied that the included studies had quantified four microstate classes. The fact that the meta-analysis across those studies yielded evidence for consistent effects suggests that using four microstate classes has empirical justification and that these should be considered in future studies.

The main significant findings of the meta-analysis were related to microstates of classes C and D: microstates of class D were consistently found to cover less of the total time and showed a reduction in its mean duration, while microstates of class C covered more of the total time and occurred more frequently. There was also evidence for a weak effect in microstates of class B, where a shortening was observed. These effects could not reasonably be explained as side effects of medication upon the EEG, because they persisted when studies with medicated patients were excluded.

It has to be noted that our sample included one study with individuals at risk for developing schizophrenia [carrying the 22q11.2 deletion syndrome (27)]. This study showed the same microstate abnormalities in these individuals as in schizophrenia patients. This supports the view that microstate analysis can provide information of potential clinical value and could be considered useful for monitoring neuropsychiatric disorders.

There is an additional external support for the conclusion that in particular, microstate classes C and D relate to brain functions affected in schizophrenia patients: a large developmental study with healthy subjects found that during late adolescence, and thus during the typical age of onset of schizophrenia, microstate class D was found to be reduced compared to other life periods, while microstate C was most prominent in that phase of development

(29). The above conclusion also receives support from interventional studies: Yoshimura et al. (36) found an increased duration in microstates of class D in healthy controls after a pharmacological intervention with a low dosage of an antipsychotic drug (perospirone) taken by healthy volunteers, indicating that the drug may counteract the microstate abnormalities observed in schizophrenia. In the study by Kikuchi et al. (13), EEG microstates were quantified in patients with schizophrenia before and after treatment with antipsychotic medication. In general, patients showed the above outlined pattern of increased C and decreased D microstate classes before treatment. When analyzing the microstates after treatment, this pattern had normalized selectively in those patients who responded well to the antipsychotic treatment, whereas patients with a poor response showed little change. In accordance with this findings, there was a strong negative correlation ($r = -0.71$) between the change of the symptoms and microstate class D duration, and a strong positive correlation between change of symptoms and microstate class C occurrence [$r = 0.72$ (13)].

Finally, in the domain of psychopathological symptoms, the paper by Koenig et al. (23) reported a negative correlation between microstates of class D duration and a score of paranoid-hallucinatory symptomatology, and Kindler et al. (37) could show that in schizophrenic patients with frequent auditory verbal hallucinations, shortening of microstate class D was associated with the acute experience of hallucinations.

Comparison with Other Electrophysiological Indices of Schizophrenia

The effect sizes estimated in this meta-analysis of the currently available studies on EEG resting-state microstates lay between those found for spectral changes in resting-state EEG, and those found for amplitudes and latencies of various event-related potential (ERP) components: based on a total of over 1000 patients and controls each, a meta-analysis of spectral EEG indices indicated an effect size of 0.46 for an increase of delta band activity and an effect of 0.42 for an increase of theta band activity (38). Meta-analyses of ERP markers of schizophrenia showed larger effect sizes across rather different paradigms: P50 amplitude indices of sensory gating yielded effect sizes between −0.93 (39) and −1.56 (40), and the estimated effect size across studies using mismatch negativity type experiments was 0.99 (41). In studies that involved participants in active tasks, the effect size was estimated to be −0.83 for P300 abnormalities (42) and 0.82 for the N400 latency (43). Our intermediate effect size result may indicate that compared to frequency domain EEG indices, microstate analysis succeeds better in distinguishing between brain processes that are, or are not relevant for schizophrenia, but not to the same degree as some of the averaged evoked potentials do. However, by considering task-related activity as a state-dependent process, it follows that a particular type of resting-state abnormality may explain abnormal task responses in a broader range. Resting-state abnormalities may thus be causally "up-stream" of task-state abnormalities and hence become particularly interesting for an integral understanding of the observed psychopathology.

What Is Known about the Function of the Affected Microstate Classes in Relation to Schizophrenia?

Microstates of class D have been attributed to flexible aspects of attention, such as switching and reorientation of attention to relevant information, because it has been associated with the frontoparietal attention network found in fMRI-BOLD data (19). Additionally, microstates of class D have been shown to be reduced in certain mental states, such as hypnosis (44), sleep (31), or during the acute phase of hallucinations (37). Noteworthy, all of these states are reality remote. This leads to the assumption that microstates of class D might be related to the updating of mental content based on internal and external information that is close to reality. The fact that our meta-analysis yielded evidence for an impairment of microstates of class D in patients with schizophrenia can thus be linked to deficits in attentional processes, context update, and executive control, where core deficits have long been identified in schizophrenia (45).

Microstate of class C, which, in contrast to microstates of class D, consistently occurred more often and covered more overall time in patients compared to healthy controls has been associated with the saliency network: areas found in fMRI studies that were associated with microstates of class C overlapped with the saliency network in the anterior cingulate, the inferior frontal gyrus, and the insula (19). Furthermore, an increase in microstates of class C has been found during hypnosis (44), which is a state often associated with the experience of saliency. Associating the increased occurrence of microstates of class C in schizophrenia with salience-related processes dovetails with the view that schizophrenia is a state of aberrant assignment of salience "at a mind level" (46).

The negative correlation between microstates classes C and D presence leads to the assumption of a balance between these states, with antagonistic functional roles: in conditions that demand an ongoing integration of contextual information, such as normal wakeful rest in healthy adults, microstates classes C and D explain an approximately equal part of the ongoing brain electric activity. However, microstates of class C become more dominant while ties to contextual information are loosened, i.e., during sleep, hypnosis, or psychosis, whereas microstates class D's contribution is reduced. We may thus interpret the overall picture of our findings as an imbalance between attentional and saliency-related processes in schizophrenia patients. Interestingly, this observation is also supported by converging findings in two studies that analyzed the transitions between microstates (microstates syntax). We are particularly interested in their findings regarding microstates classes C and D in patients with schizophrenia or at risk for schizophrenia (28, 33): whereas healthy controls showed more than the expected transitions from C to D, patients showed these transitions less than expected, but there were more than expected transitions from D to C (28, 33). We may thus conclude that the research on microstates in schizophrenia yields a consistent picture of an imbalance between processes that integrate contextual information, which are reduced, and processes that load on saliency, which are increased.

Only little is known about microstates of class B. Britz et al. (19) related microstates of class B to the resting-state visual network in fMRI. In its role in schizophrenia patients, however, the results so far are inconsistent: two papers (21, 33) found a significant shorter duration, whereas one study (26) has reported significant more coverage of microstates of class B in patients compared to healthy controls, which would counteract an effect of shortening. In addition, the fact that the findings in microstate where not significant after correcting for multiple testing casts further doubt on the relevance of this effect.

Implications and Future Directions

Cognition is subject to adaptive changes based on the external and internal needs. Furthermore, both cognitive resources and brain microstates are age-dependent and presumably undergo experience-dependent plastic changes (29). This may imply that microstates can be influenced by mental training such as NFB. Previously published studies have repeatedly shown that it is feasible to modulate stimulus-related EEG brain potentials with NFB in patient populations (47–49). In schizophrenia, Schneider et al. (50) found that patients were able to have conscious control of slow cortical potentials but no clinical changes were reported. Similarly, Gruzelier et al. (51) showed the capability of schizophrenic patients in learning a control task and demonstrated the feasibility of operant conditioning based on the EEG. Recently, one case series using EEG (52) and one study on resting-state fMRI (53) were published on NFB with schizophrenia patients. Both studies demonstrated learning.

The first indication of the ability of self-regulation of microstates of class D in a NFB-training in healthy controls has been shown by Diaz Hernandez et al. (32). All of the 20 trained subjects increased the percentage of time spent producing microstate D in at least one of the investigated NFB success indices. However, it remains to be seen if such a NFB training is also feasible in patients with schizophrenia and whether such a training would have a clinical effect.

The present study gave an overview of the few existing studies on brain microstates in schizophrenia that have accumulated over the last 15 years. Given the small number of studies that has been done so far, an enlargement of the sample size in future studies is essential. Furthermore, the heterogeneity of the included subjects in terms of medication and diagnosis gives reason to a cautious interpretation of the presented results. Nevertheless, despite small samples and heterogeneous subjects, we found consisting results with the included studies, which justifies further investigation of microstate classes C and D as state markers of acute schizophrenia and the attempt to modulate them (e.g., with help of NFB) as a possible add-on treatment.

AUTHOR CONTRIBUTIONS

KR, LDH, AB, and TK: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This study was supported partly by the Swiss National Science Foundation (Sinergia Grant #136249 and DocMobility Grant #P1BEP3_158984) and the Jacobs Foundation (#36-663).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2016.00022

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 19 October 2015
doi: 10.3389/fpsyt.2015.00149

Attentional load effects on beta oscillations in healthy and schizophrenic individuals

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Attentional deficits are prominent among the cognitive disturbances found in schizophrenia. Given that schizophrenia is also characterized by abnormalities in high-frequency oscillations, we investigated whether attentional function in schizophrenia is related to abnormalities in high-frequency oscillations in a visual discrimination task in which attentional load was manipulated. Sixteen healthy control subjects (HC) and 23 chronic schizophrenia patients (SZ) discriminated between target discs ($p = 0.2$) and standard discs ($p = 0.8$). Attentional load was manipulated by varying the size difference between the target and standard discs across blocks: large (Easy condition), medium (Medium), and small (Difficult). The electroencephalogram was recorded and the oscillations evoked by the standard stimuli were analyzed using the Morlet wavelet transform. Subjects' performance decreased as attentional load increased, but HC and SZ did not differ. Attentional load increased β phase-locking factor at frontal, parietal, and occipital electrode sites in HC but not SZ. In SZ, however, there was a correlation between the β attentional load effect and overall d', indicating that high-performing SZ had relatively normal β attentional load effects. These results show that variations in attentional load are associated with β oscillations and provide a link between attentional dysfunction and β-generating neural circuitry in schizophrenia.

Keywords: schizophrenia, electroencephalogram, gamma oscillation, beta oscillation, attention

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Junfeng Sun, Shanghai Jiao Tong University, China
Avinash Ramyead, Universitäre Psychiatrische Kliniken Basel, Switzerland

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Specialty section:
This article was submitted to Neuropsychiatric Imaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *17 July 2015*
Accepted: *05 October 2015*
Published: *19 October 2015*

Citation:
Ghorashi S and Spencer KM (2015) Attentional load effects on beta oscillations in healthy and schizophrenic individuals. Front. Psychiatry 6:149. doi: 10.3389/fpsyt.2015.00149

INTRODUCTION

A growing body of evidence implicates high-frequency oscillatory activity in the electroencephalogram (EEG) in various aspects of attention. Studies of animals [e.g., Ref. (1–3)] and humans [e.g., Ref. (4–6)] have shown that attention is associated with enhanced β (13–30 Hz) and γ (30–100 Hz) band oscillations. These high-frequency oscillations also appear to be involved in the control of attention, possibly coding templates of attended features in attentional control areas and transmitting bias signals from control areas to sensory areas via long-distance synchronization (7–9).

Attention deficits are prominent among the cognitive disturbances that are typically found in individuals with schizophrenia (10, 11). Schizophrenia is also characterized by abnormalities in high-frequency oscillations associated with both sensory/perceptual processing [e.g., Ref. (12–20)] and cognitive control processes [e.g., Ref. (21–23)]. These abnormalities have been proposed to originate in disturbances of cortical microcircuitry, such as in recurrent inhibition from fast-spiking, parvalbumin-expressing interneurons to pyramidal cells (24). One question that has not yet been

addressed is whether attention deficits in schizophrenia are related to abnormalities in high-frequency oscillations. Here, we tested this hypothesis by examining how oscillatory activity in chronic schizophrenia patients (SZ) and matched healthy control subjects (HC) was affected by varying the attentional load of a simple visual discrimination task [cf. Ref. (25)]. Subjects performed a visual oddball task in which they discriminated between standard stimuli of a constant size and target stimuli that varied in size across blocks. As the target/standard discrimination became more difficult, the attentional load of the task increased.

MATERIALS AND METHODS

Subjects

This study was approved by the Institutional Review Boards of the Veterans Affairs Boston Healthcare System and Harvard Medical School. Written informed consent was obtained from the subjects after the study was described to them. All subjects were paid for their participation in the study.

Subjects were 16 HC (two female) and 23 SZ (one female). SZ were recruited from outpatient clinics at the Veterans Affairs Boston Healthcare System. SZ were diagnosed based on the Structured Clinical Interview for DSM-IV [SCID (26)] and medical record review. HC were recruited from the Boston metropolitan area and matched the SZ at the group level on age, handedness (27), parental socioeconomic status [PSES (28)], gender proportion, and estimated premorbid intelligence, as assessed by performance on the Reading scale of Wide Range Achievement Test [WRAT-3 (29)]. See **Table 1** for demographic and clinical characteristics. Clinical symptoms were assessed using the Scale for the Assessment of Positive Symptoms [SAPS (30)] and the Scale for the Assessment of Negative Symptoms [SANS (31)]. Medication dosage in chlorpromazine equivalents was calculated using the conversion factors of Stoll (32) and Woods (33).

Exclusion criteria for all subjects were (1) left-handedness, (2) history of electroconvulsive shock therapy, (3) history of neurological illness including epilepsy, (4) lifetime history of substance dependence or history of substance abuse within the past 5 years, (5) history of steroid use, and (6) estimated premorbid intelligence quotient (WRAT-3 score) below 75. Additional exclusion criteria for HC were the presence of an Axis-I disorder [from the SCID-Non-Patient edition (34)], and having a first-degree relative with an Axis I disorder.

TABLE 1 | Demographic and clinical data and between-group comparisons for the healthy control (HC) and schizophrenia patient (SZ) groups.

	HC ($N = 16$)	SZ ($N = 23$)	Statistic	p
Age (years)	41.3 ± 5.0	42 ± 9.6	$t_{(37)} = -0.26$	0.81
Parental socioeconomic status	2.6 ± 1.1	2.6 ± 1.0	$t_{(37)} = 0.05$	0.96
WRAT-3	49.31 ± 5.52	47.64 ± 4.61	$t_{(36)} = 0.988$	0.33
Age of onset (years)		24.3 ± 6.6		
Positive symptom total (SAPS)		9.4 ± 3.4		
Negative symptom total (SANS)		10.5 ± 6.2		
Medication dosage (chlorpromazine equivalent)		365.8 ± 379.6		
		Range: 100–1467		

Mean ± SD are given for each variable.
WRAT-3, Wide Range Achievement Test; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

Stimuli and Procedure

To study the effects of attentional load, we used an oddball task in which the difficulty of discriminating target from standard stimuli was varied across blocks (Easy, Medium, and Difficult conditions). Targets and standards differed in size, and the size of the targets was varied while the size of the standards was kept constant. As the responses to standards provide measures of brain activity that do not include motor- or deviance-related activity (as do the responses to targets), attentional load should be the only factor that would affect the responses to standards. On each trial, subjects classify the stimulus as a standard or a target, which involves allocating attentional resources to the comparison of the stimulus percept with templates of the targets and standards in working memory. As the comparison becomes more difficult (the size of standards and targets becomes more similar), more attentional resources must be allocated to the comparison process.

Stimuli were white discs presented on a black background at the center of the screen. The diameter of the standard discs was 3.28° of visual angle, and the diameters of the target discs in the Easy, Medium, and Difficult conditions were 2.28°, 2.46°, and 2.64° of visual angle, respectively (**Figure 1**).

Subjects performed three blocks of 180 trials each: Easy (the greatest size difference between the target and the standard discs), Medium, and Difficult (the smallest size difference between the target and the standard discs). On 144 (80%) of those trials, the standard disc was displayed and on the rest of the trials (20%) the target was displayed. Standard and target trials were presented in pseudorandom order. The order of the blocks was counterbalanced across subjects. Each block of trials was preceded with practice trials to familiarize the subjects with the difficulty of the required target/standard discrimination.

Subjects were seated at a distance of 1 m from the monitor (nasion to the central fixation point). Stimuli were presented for 82 ms with an inter-stimulus interval of 1058 ms (onset-to-onset). Subjects were instructed to respond only to the targets by pressing

FIGURE 1 | Stimuli in each condition of the experiment and their sizes in degrees of visual angle: the standard disc (left) and target discs in the Easy, Medium, and Difficult conditions.

a key on the response pad with their right hand as quickly and accurately as possible.

EEG Acquisition and Analysis

The EEG was recorded with a Biosemi ActiveTwo system using active electrodes in an electrode cap at 71 standard EEG and electro-oculogram (EOG) sites (DC–100 Hz bandpass filter, 512 Hz digitization rate). The DC offsets were kept below 25 mV. During data acquisition, all channels were referred to the system's internal loop (CMS/DRL sensors located in the parietal region) and off-line re-referenced to the left mastoid electrode. The bipolar vertical EOG was derived from electrode Fp1 and an electrode below the left eye. The horizontal EOG was derived from electrodes on the left and right outer canthi.

For each of the 540 trials presented to each subject, a 1000-ms epoch was extracted from 500 ms pre-stimulus to 498 ms post-stimulus using BrainVision Analyzer 1.0 (Brain Products GmbH). Further processing was performed using software in MATLAB (Mathworks, Inc.) and IDL (Exelis Visual Information Solutions, Inc.). Error trials were excluded from processing, and an initial artifact detection scan was run. The artifact exclusion criteria were (1) $>\pm 90$ μV change in one time point and (2) amplitude range within an epoch exceeding 200 μV. Then independent component analysis [implemented in the *runica.m* program from EEGLAB (35)] was used to remove ocular and muscle artifacts. Independent components representing artifacts were identified based on their characteristic topographic, temporal, and spectral signatures (36–38). Next, a second artifact detection scan was run. Finally, the retained correct-response, artifact-free epochs were re-referenced to the average reference (39), computed on all 68 scalp channels, excluding the EOG channels. The number of epochs retained per subject was (mean ± SD) 493 ± 31 for HC and 485 ± 47 for SZ, and these numbers did not differ [$t_{(37)} = 0.596$, $p = 0.56$]. None of the subjects had more than 1/3 of trials per condition rejected.

EEG analyses focused on the responses to standard stimuli, which were physically identical in each condition and not influenced by target- or response-related processing. Event-related potentials (ERPs) and spectral measures were computed from the artifact-free single-trial epochs. Time-frequency decomposition was performed using the Morlet wavelet transform (frequency/duration ratio $f_0/\sigma_f = 6$), applied in 1 Hz steps from 4 to 100 Hz at each time point to yield time-frequency (TF) maps of phase-locking factor (PLF) values (40). PLF is computed as one minus the circular variance of phase (at each time point and wavelet frequency) across the set of single trials in a condition for each subject. This measure reflects the degree to which a set of signals match in phase, or are phase-locked, relative to a reference time point (such as stimulus onset or RT). PLF values range from 0 (no synchrony, random distribution of phases) to 1 (perfect synchrony, same phase on every trial). (We also measured evoked power but do not report it here, as it yielded a very similar but weaker pattern of results as PLF. Analyses of total power did not reveal any effects of group or attentional load.) Average pre-stimulus baseline values from −100 to 0 ms were subtracted from the PLF TF maps.

Statistical Analyses

Statistical non-parametric mapping (SnPM) was used to find clusters of TF elements (time points at each frequency) in which there was a significant interaction between the factors Group (HC/SZ) and Difficulty (Easy/Difficult). This approach, based on the permutation test, has several advantages over parametric statistical tests (41, 42), particularly that it does not rely upon assumptions about the statistical distribution of the data. Thus, the SnPM approach is more sensitive than parametric tests when the assumptions underlying the latter are not met (e.g., normality), which is likely for the PLF measure. Additionally, the permutation test provides control for multiple comparisons, since all the TF elements are permuted in parallel. In practice, we found it necessary to apply additional criteria to control for multiple comparisons. Our SnPM approach consisted of the following steps:

(1) TF *t*-maps were computed by performing *t*-tests on each TF element across the epoch for each channel. The Group × Difficulty interaction map was computed with between-groups *t*-tests on the Difficult minus Easy difference maps, which is equivalent to a 2 × 2 ANOVA design.
(2) TF maps of *p* values were computed for each *t*-map using the permutation test ($\alpha = 0.05$, two-tailed, 1000 permutations). A difference map (Difficult minus Easy) was computed for each subject, and the assignment of subjects to the groups was shuffled on each permutation. The *p* value of each TF element was obtained by determining the percentile rank of the observed *t* value in the shuffled *t* distribution.
(3) The resulting *p*-maps were thresholded at $p > 0.975$ for positive interactions (HC difference > SZ difference) and $p < 0.025$ for negative interactions (SZ difference > HC difference). TF elements with *p* values above/below these thresholds were retained only if they were part of a cluster with a duration of at least one cycle of the respective frequency (e.g., 25 ms for a 40 Hz cluster).
(4) The thresholded *p*-maps were summed across the scalp EEG channels ($N = 68$) to create a channel sum histogram of TF clusters. This histogram represents the number of channels on which each TF cluster was found. The channel sum histogram was then thresholded at the 95th percentile of the distribution for that histogram, retaining only clusters in which the number of contributing channels was at the upper 5% of the distribution. The reasoning for this step was that since a large number of clusters occurred at only one electrode, "true" effects should be present on multiple channels due to volume conduction.
(5) A one-cycle duration cutoff was applied again to the channel sum histogram, so that all the final TF clusters were at least one cycle in duration at their respective frequencies. The electrodes contributing to each cluster were plotted in topographic maps with color codes indicating the percentage of the cluster area to which the electrode contributed.

Task performance was measured with error rate, median reaction time (RT), and the signal detection measure *d′*

(discriminability), which measures subjects' ability to discriminate between stimulus classes independently of biases to respond to one class over the other (43). PLF of visual-evoked γ oscillations was measured at electrodes and latency windows determined from the grand averages. Performance measures and PLF were analyzed with analysis of variance (ANOVA) in the design Group (HC/SZ) × Difficulty (Easy/Medium/Difficult) [×Hemisphere (Left/Right) × Electrode factors, where relevant]. The Greenhouse–Geisser correction for inhomogeneity of variance (44) was applied for factors with more than two levels and is reflected in the reported *p* values. Correlation analyses employed the non-parametric Spearman's ρ (two-tailed). For all statistical analyses, $\alpha = 0.05$.

RESULTS

Task Performance

In general, subjects' performance decreased as the difficulty of the target/standard discrimination increased (**Figures 2A–C**). Subjects' error rates increased with Difficulty ($F_{2,74} = 5.61$, $p < 0.05$). The HC and SZ groups were not significantly different in overall error rate ($F_{1,37} = 1.09$, $p = 0.30$), and the Group × Difficulty interaction was not significant ($F_{2,74} = 1.09$, $p = 0.33$). Subjects' median RTs also increased with Difficulty ($F_{2,74} = 5.77$, $p < 0.01$), but the two groups did not have significantly different overall RTs ($F_{1,37} < 1$, *ns*), and the Group × Difficulty interaction ($F_{2,74} = 1.54$, $p = 0.22$) was not significant.

Analyses of d' indicated that overall, subjects' discrimination between targets and standards decreased as Difficulty increased ($F_{2,74} = 12.49$, $p < 0.001$). HC and SZ did not differ significantly in overall d' ($F_{1,37} < 1$, *ns*), and there was no significant Group × Difficulty interaction ($F_{2,74} = 2.56$, $p = 0.09$). Thus, as the size of the target stimulus approached the size of the standard stimulus, the difficulty of the target/standard discrimination increased for both groups.

Event-Related Potentials

No effects of task difficulty were apparent in the ERPs for either subject group (see **Figure 3**), and the ERPs were not analyzed further.

Oscillatory Activity

Statistical non-parametric mapping of the PLF data revealed two Group × Difficulty clusters, both with relatively long latencies and in the β frequency range (**Figure 4D**). Cluster 1 occurred at 328–377 ms in the 26–27 Hz frequency band, and had contributions mainly from frontal, occipital, and occipital-temporal electrodes (AF4, AF8, F6, FCz, FT8, CP1, P9, PO8, Oz, O2, and Iz) (**Figure 4E**, left). Using this cluster as a region of interest, we analyzed PLF in a full ANOVA with the design Group × Difficulty × Electrode. PLF increased with Difficulty in

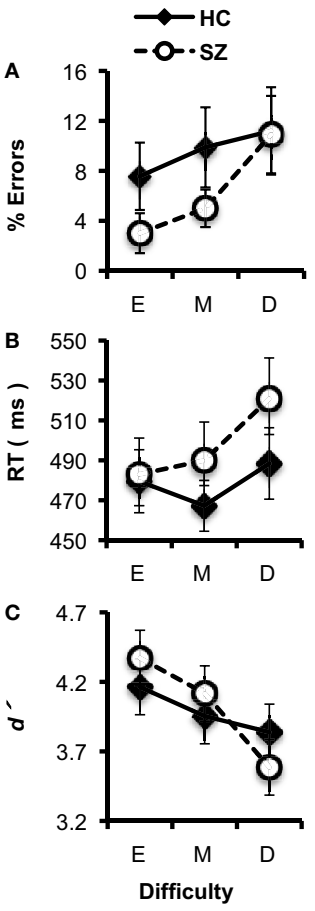

FIGURE 2 | Task performance data (error bars indicate SE) for the healthy control (HC) and schizophrenia patient (SZ) groups in the three experimental conditions (E: Easy; M; Medium; D: Difficult). **(A)** Error rates. **(B)** Median reaction time (RT). **(C)** d'.

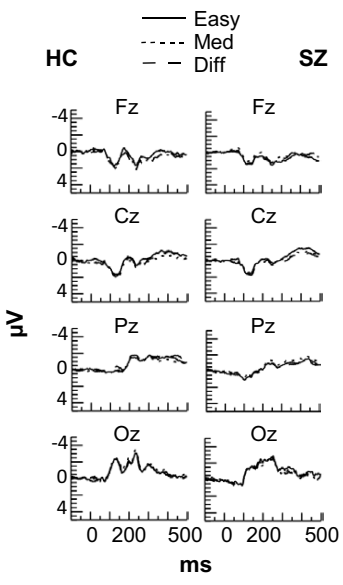

FIGURE 3 | Grand average event-related potentials at frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) electrode sites in each Difficulty condition for the HC and SZ groups. No effects of Difficulty were observed for either group.

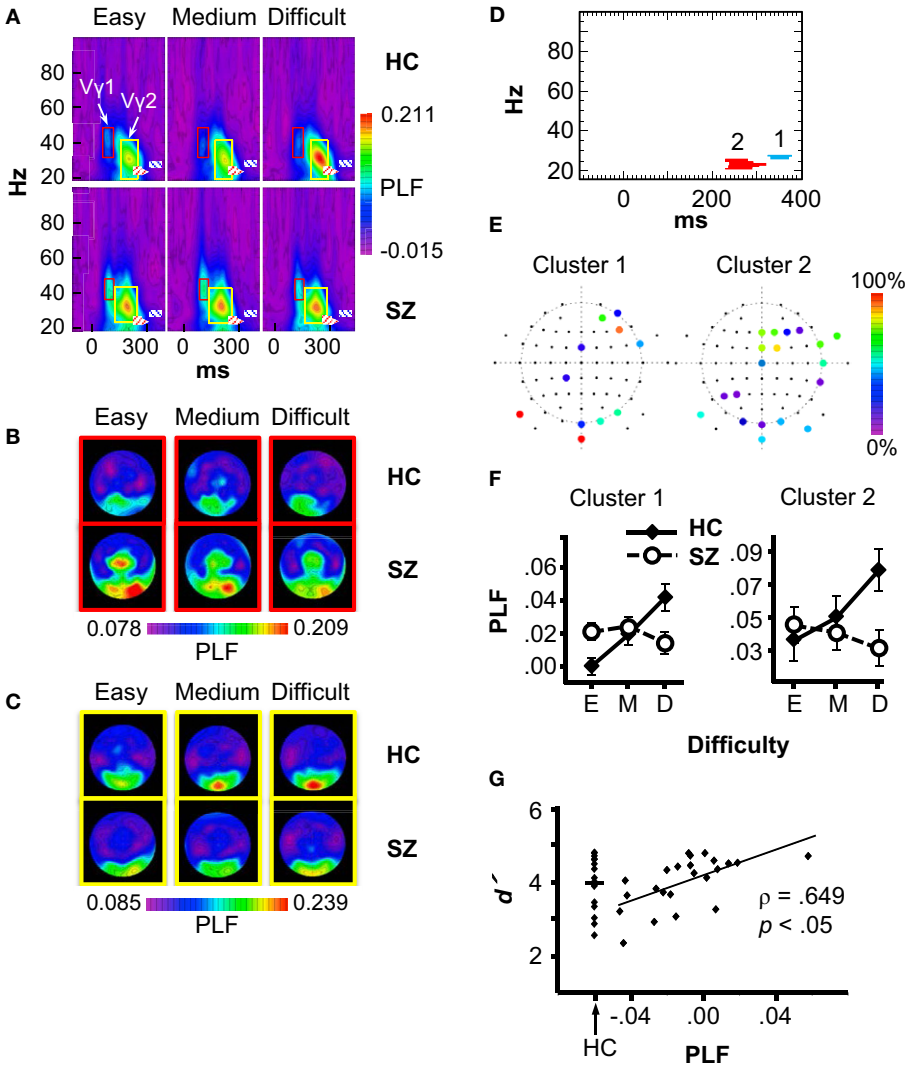

FIGURE 4 | Phase-locking factor (PLF) data. **(A)** Grand average time-frequency (TF) PLF maps for the HC and SZ groups in each Difficulty condition. TF maps were averaged across all scalp electrodes. Boxes indicate the ranges in which the Vγ1 (red boxes) and Vγ2 (yellow boxes) oscillations were measured. Crosshatched boxes represent Cluster 1 (blue) and Cluster 2 (red) derived from statistical non-parametric mapping. **(B)** Topography of Vγ1 in each condition and group. **(C)** Topography of Vγ2 in each condition and group. **(D)** Statistical non-parametric mapping results showing the two Group × Difficulty PLF clusters (Cluster 1: 328–377 ms, 26–27 Hz; Cluster 2: 232–320 ms, 21–25 Hz). **(E)** Cluster topographies. The color scale indicates the percentage of the cluster to which each electrode contributed. **(F)** PLF values for each cluster in three difficulty conditions (E: Easy; M: Medium; D: Difficult). **(G)** Scatterplot of the correlation between the Cluster 1 Difficulty effect (Difficult minus Easy PLF) and overall *d′* in the SZ group. The distribution of *d′* values for HC is shown for comparison.

HC ($F_{2,30} = 7.51$, $p < 0.01$), but this effect was not significant in SZ ($F_{2,44} = 2.52$, $p = 0.09$), and these patterns differed between groups (Group × Difficulty: $F_{2,74} = 11.43$, $p < 0.001$) (see **Figure 4F**, left). The main effect of Difficulty was also significant ($F_{2,74} = 4.24$, $p < 0.05$).

Cluster 2 occurred at 232–320 ms and 21–25 Hz, with contributions from frontal, temporal, parietal, and occipital electrodes (Fz, F2, F4, F6, FCz, FC2, FT8, FT10, Cz, T8, TP8, P3, P5, P9, PO10, Oz, O1, O2, and Iz) (**Figure 4E**, right). Like Cluster 1, Cluster 2 PLF increased with Difficulty for HC ($F_{2,30} = 12.09$, $p < 0.01$), but this effect was not significant in SZ (SZ: $F_{2,44} = 1.91$, $p = 0.16$; Group × Difficulty: $F_{2,74} = 12.43$, $p < 0.001$) (see **Figure 4F**, right). The main effect of Difficulty approached significance ($F_{2,74} = 3.03$, $p = 0.057$). Neither of the β effects was correlated with medication dosage (Cluster 1: $\rho = 0.12$, $p = 0.65$; Cluster 2: $\rho = -0.05$, $p = 0.85$). Exploratory correlations between the β effects and clinical symptoms did not reveal any significant associations.

To determine whether the β attention effects were related to subjects' task performance, we computed correlations between the PLF effect (Difficult minus Easy) for Clusters 1 and 2 (averaged over the electrodes contributing to each cluster) with task performance measures (Difficult minus Easy effects and overall means for RT, error rate, and *d′*). The *p* values of the correlations were Bonferroni-corrected (6 measures × 2 TF clusters × 2

subject groups). This analysis revealed (**Figure 4G**) a significant correlation for Cluster 1 in the SZ group between the PLF effect and overall d' ($\rho = 0.649$, $p < 0.05$ corrected). The correlation was still significant after excluding one outlier subject ($\rho = 0.63$, $p < 0.05$ corrected). The range of the PLF effect varied from negative (Easy > Difficult) to positive (Difficult > Easy) across SZ. Thus, SZ who were better able to discriminate targets and standards in general had more normal (positive and larger) β attentional load effects.

Although effects of subject group and attentional load were not found on the stimulus-evoked γ oscillations in the statistical maps, since stimulus-evoked γ oscillations can be modulated by attention [e.g., Ref. (2, 5)], and visual γ deficits have been reported in schizophrenia (reviewed above), we analyzed the γ oscillations evoked by the standard stimuli to confirm these results. Standard stimuli evoked an early visual γ oscillation (Vγ1), which was measured at the occipital and occipito-temporal electrodes P9/10, PO7/8, PO9/10, and O1/2. The frequency range for Vγ1 was 33–48 Hz for HC and 36–48 Hz for SZ, and the time range was ~68–116 ms after stimulus onset for HC and ~80–116 ms for SZ (see **Figure 4A** red boxes, and **Figure 4B**). Vγ1 PLF did not differ between groups ($F_{1,37} = 2.26$, $p = 0.14$), nor was it modulated by task difficulty ($F_{2,74} = 1.09$, $p = 0.34$). The Group × Difficulty interaction was also not significant ($F_{2,74} = 1.51$, $p = 0.23$).

A later γ oscillation (Vγ2) with a similar scalp topography as Vγ1 was also observed, and was measured at the same electrodes as Vγ1. The frequency range for Vγ2 was 19–42 Hz for HC and 23–44 Hz for SZ, and the time range was ~146–269 ms after stimulus onset for HC and ~122–250 ms for SZ (**Figure 4A** yellow boxes, and **Figure 4C**). Vγ2 PLF was not significantly different between groups ($F_{1,37} < 1$, *ns*), nor was it modulated by task difficulty ($F_{2,74} < 1$, *ns*), and the Group × Difficulty interaction was not significant ($F_{2,74} = 1.29$, $p = 0.28$). Thus, the visual-evoked γ oscillations were not affected by attentional load, nor did they differ between subject groups.

DISCUSSION

We investigated how oscillatory activity in HC and SZ was affected by increasing the attentional load of a visual discrimination task. Increased attentional load in HC was manifested as increased stimulus-locked β activity at electrodes over cortical areas involved in attentional control and visual processing. In SZ, these β effects were not apparent at the group level, indicating an overall absence of attentional modulation of β. However, across SZ the later β effect was correlated with overall d' values, such that those patients with a more normal late β effect were better able to discriminate targets from standards in general. It is important to note that SZ did not differ from HC in their overall ability to perform the task, as there were no group differences in error rate or RT. Therefore, the absence of attentional modulation of β activity in SZ at the group level cannot be attributed simply to a general deficit. Rather, the pattern of results suggests that attentional modulation of β activity is dysfunctional in schizophrenia overall but varies across individuals such that it is relatively preserved in SZ with better attentional function.

The β oscillation effects we observed were associated with changes in task difficulty, which modulated the attentional load of the task. As the β effects were found for the standard stimuli, they were unrelated to physical stimulus differences between conditions or manual response effects. Since the β effects occurred at relatively late latencies (232–377 ms), after the completion of several early stages of sensory and perceptual processing (i.e., those indexed by the C1, P1, and N1 ERP components and the Vγ1 oscillation), they are unlikely to reflect simple attentional modulation of sensory processes. While the inferences that can be drawn from scalp topographies regarding the neuroanatomical localization of EEG effects are limited, we note that the β effects were present at electrode sites over cortical areas involved in attentional control (frontal and parietal cortex), as well as visual cortex, and the right hemispheric lateralization of the β cluster topography is consistent with the right hemisphere's predominant role in sustained attention [e.g., Ref. (45)]. One hypothesis regarding the functional significance of these oscillations is that they reflect attention-dependent processes by which a template of the target stimulus in short-term memory is compared with the current stimulus. This interpretation of the β effects is consistent with the hypothesis of Engel and Fries (46) that the role of β oscillations in top-down control is to maintain the current sensorimotor or cognitive state. β oscillations have been linked to cognitive domains, such as working memory [e.g., Ref. (47–49)], perceptual decision making [e.g., Ref. (50–53)], and attention (1, 3, 4, 7). Furthermore, computational modeling suggests that some β oscillations (although at lower frequency than found here) may be well suited for maintaining cell assembly states as required by working memory (54).

The finding that attentional modulation of β activity was dysfunctional in SZ suggests that neural circuit abnormalities in schizophrenia may extend to the infragranular layers of the cortex. There is evidence that β oscillations are generated in the deep layers of sensory and association cortex, while γ oscillations are generated in the granular and superficial layers [e.g., Ref. (55–57)]. Deficits of γ oscillations in schizophrenia have been hypothesized to be related to abnormalities in the function of inhibitory interneurons in the upper cortical layers, particularly the parvalbumin-expressing, fast-spiking class (24). The possible neural circuit abnormalities that could be responsible for the β deficit here are not as clear. The present β effects were found at electrodes lying over associational areas involved in attentional control, as well as visual cortex. Roopun et al. (57) found that β oscillations generated in layer 5 of sensory and association cortices arose from very different mechanisms, even though the frequency characteristics of those oscillations did not differ between areas. Sensory cortex β was generated by a circuit composed of pyramidal cells and electrically coupled low-threshold spiking interneurons. In contrast, association cortex β was generated by intrinsically bursting pyramidal cells in layer 5 that are synchronized through gap junctions.

The visual-evoked γ oscillations were not affected by attentional load (as with the ERPs), nor did they differ between SZ and HC. The literature on SZ deficits in visual γ oscillations has mixed findings. While some studies have reported reductions of power and/or PLF of visual γ in SZ (12, 13, 15–18, 20),

other studies have not found deficits (14, 19), and increased γ has been reported in SZ (58) as well as schizotypal individuals (59). The factors responsible for the variance in the reported findings are not yet clear, but it can be concluded that there is not a general deficiency of γ generation in the visual cortex in schizophrenia.

Some limitations of this study are clear. One issue is that the SZ had been taking antipsychotic medications for many years, so the degree to which antipsychotics may have influenced the findings is unknown, despite our efforts to assess such possible effects by correlating with chlorpromazine equivalents. Another is that small effects of attention on γ oscillations may not have been detectable due to the sample sizes used here.

This study demonstrates that attentional load effects are manifested in healthy individuals as β activity over areas involved in attentional control and stimulus representation. Individuals with chronic schizophrenia, however, show abnormal β attentional load effects, suggesting that β-generating circuits may constitute part of the neural substrates underlying the cognitive control deficits that figure prominently in this disorder (60, 61). We note that there is also prior evidence for β oscillation abnormalities in SZ: Uhlhaas et al. (19) reported evidence of reduced inter-regional β synchronization during Gestalt perception, and Krishnan et al. (13) found reduced visual steady-state responses to β frequency stimulation. Therefore, the investigation of β oscillations may provide new insights into the neural circuit abnormalities that underlie schizophrenia.

ACKNOWLEDGMENTS

This study was supported by a U.S. Department of Veterans Affairs Merit Review grant (I01 CX000154); grants R03 MH076760, R01 MH080187, and R01 MH093450 from the U.S. National Institutes of Health; and a NARSAD Young Investigator Award to KS.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 26 April 2016
doi: 10.3389/fpsyt.2016.00074

Optical Topography in Psychiatry: A Chip Off the Old Block or a New Look Beyond the Mind–Brain Frontiers?

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Keywords: optical topography, NIRS, psychiatry, mind–brain, neuroimaging

THE PSYCHIATRIC BOTTLENECK

Psychiatric conditions that include depression, schizophrenia, and dementia contribute most significantly to overall disability adjusted life years (DALYs), surpassing both cardiovascular disease and cancer (1, 2). Therefore, timely and accurate diagnosis and treatment are crucial in psychiatric disorders, for which the development of specific biomarkers would be of particular importance. Despite advances in the field of Psychiatry with more comprehensive classification and description of diagnostic criteria, a pathophysiologically oriented classification of psychiatric disorders based on neurobiological basis remains elusive. The human brain with its complex integrative functions of cognition, emotional regulation, and executive function is the most challenging object of study in human science. Mental illness occurs as a result of these brain dysfunctions, but they often do not lead to distinct pathologic lesions or tissue damage. Instead, they contribute to complications in synaptic relay, synaptic plasticity, and neural circuit function, in addition to influence by external psychosocial factors. Thus, standard imaging methodologies, such as computed tomography (CT) and magnetic resonance imaging (MRI), would not be adequate to delineate the underlying abnormality contributing to the dysfunction. Our inherent lack of understanding of the mind–brain interface and the difficulty in characterizing mental illness further makes the practice of Psychiatry all the more daunting.

Being the only medical specialty without any objective diagnostic tool or marker, the current diagnostic process in Psychiatry is regretfully based on patients' reports of symptoms, observed behavior, and disease progression, which can introduce subjectivity and bias. Many clinical symptoms are also common to various psychiatric disorders, such as depressive symptoms in unipolar depression, bipolar disorder, schizoaffective disorder, etc., thus making it challenging to diagnose complex cases accurately within a limited time frame. This is illustrated by studies in the United States that revealed approximately 70% of bipolar patients were initially misdiagnosed due to polymorphic clinical symptoms (3, 4). It is also not uncommon to find different psychiatrists having deferring opinions about a case due to their unique experiences and training. Therefore, there is an urgent need for specific, objective biomarker-based assessments to guide diagnosis and treatment. The use of such biomarkers could assist clinicians in establishing differential diagnosis, which may improve specific individualized treatment.

EMERGENCE OF OPTICAL TOPOGRAPHY IN AN ERA OF FUNCTIONAL BRAIN IMAGING

Functional brain imaging modalities, such as functional magnetic brain imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), have

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *11 March 2016*
Accepted: *13 April 2016*
Published: *26 April 2016*

Citation:
Ho CSH, Zhang MWB and Ho RCM (2016) Optical Topography in Psychiatry: A Chip Off the Old Block or a New Look Beyond the Mind–Brain Frontiers? Front. Psychiatry 7:74. doi: 10.3389/fpsyt.2016.00074

been increasingly used over the years in research to reveal structural and functional abnormalities in psychiatric disorders. This is partly due to the increased awareness of psychiatric disorders as having a neurobiological basis and the emergence of more neuroimaging tools. Nevertheless, they have difficulty translating to bedside clinical use for diagnostic and treatment purposes due to the large machineries involved, high cost incurred, and that the assessment has to be done in very controlled artificial environments (lying still for extended periods), which potentially contributes to inconsistent and imprecise findings of functional brain alterations.

The introduction of optical topography that uses near-infrared spectroscopy (NIRS) have led to a paradigm shift in the investigation of healthy and abnormal brain functional processes within the cerebral cortex over the last two decades. Its mechanism of action, which is similar to fMRI, exploits the different absorption spectra of oxygenated and deoxygenated hemoglobin in the near infrared region, to measure changes in the concentrations of oxygenated and deoxygenated hemoglobin, thereby reflecting regional cerebral blood flow (5). Despite having limitations in spatial resolution and depth of penetration (unable to assess subcortical areas, which often play a significant role in psychiatric disorders), with confounding influence by systemic factors such as autonomic, neuroendocrine, and vascular functions, and anatomical factors, such as scalp–cortex distance, frontal sinus volume, and skin integrity (6), optical topography has several unique advantages that makes its application attractive for neuroscience and particularly psychiatric research. The device being small and portable enables assessment in the natural environment during real-life social interaction and allowing bodily movement due to its relative insensitivity to movement artifacts. This is particularly suitable for psychiatric patients who have phobia of enclosed environments and motor restlessness, and they usually prefer hassle-free procedures. It can also be applied on patients who are more severely ill who will benefit from quick measurement at the bedside, such as those in the intensive care unit. It also has good temporal resolution (less than 1 s) that is useful for characterizing the time course of brain activity. Furthermore, it can be combined with other brain imaging techniques, such as electroencephalogram (EEG), SPECT, and fMRI, to enhance the holistic understanding of functional characteristics underpinning psychiatric disorders. This device that is relatively cheap and safe can be used in clinical settings for measuring brain activity of not only adults but also children and the elderly. The fast processing of data also allows for studying of large samples.

NIRS APPLICATION IN PSYCHIATRIC DISORDERS

Over the two decades, the optical topography community has shifted from basic validation studies in healthy controls, to psychological studies focusing on visual, auditory, motor, language, and cognitive paradigms, and to the more recent phenomenological characterization of psychiatric disorders. At least 115 original articles have used NIRS to investigate psychiatric research questions by 2014 (7), and this number is expected to exponentially increase with the realization of versatile applicability of the technology and the increase in types of NIRS devices available in the market (Hitachi ETG-400, NIRScout, Artinis, etc.).

In affective disorders, frontal lobe abnormalities, particularly the decrease in bilateral frontotemporal oxygenation, have been found in unipolar depression using the verbal fluency test (VFT) (8). Some of these studies further noted frontotemporal activation to be positively correlated with adaptive coping (9) while negatively correlated with symptom severity (8). In schizophrenia, there were reduced hemodynamic responses in the prefrontal cortex of patients compared to controls (10), and was partly found to be affected by clinical characteristics such as age of onset of symptoms, medication effects, and psychopathological symptom scores, thereby inferring association between prefrontal cortex function and specific symptom dimensions (7). In personality disorders, patients with borderline personality disorders were found to have a reduced slope of task-related oxygenation increase in the left prefrontal area compared to controls when viewing sad pictures, and this had a negative association with clinical symptoms of interpersonal difficulties and fear of abandonment (11). Even in the areas of substance abuse, Schecklmann et al. revealed a reduced extent of cerebral oxygenation in the frontotemporal areas of detoxified alcohol-dependent patients despite having normal VFT performance, which may precede behavioral or cognitive deterioration with a later onset (12). Other disorders, such as anxiety, autism, attention-deficit hyperactivity disorders, dementia, and eating disorders, have also been studied using NIRS, which revealed intriguing findings that warrants further investigation.

Beyond the use of NIRS in studying phenomenological characterization of disorders, it has also been trialed as a treatment tool, such as in the use of neurobiofeedback to enhance efficacy of mental practice with motor imagery (13). It has also been combined with other treatment modalities, such as transcranial magnetic stimulation (TMS) (14) and trancranial direct current stimulation (15), to monitor treatment effects. With the creative use of both neurostimulation and imaging, it opens up new opportunities for neurocognitive augmentation and remediation.

With psychiatric disorders being strongly predisposed by genetic factors with estimated heritability for schizophrenia, bipolar disorder, and autism being much higher than that of diseases, such as breast cancer and Parkinson disease (16), this leads to an integrated research method known as imaging genetics, which uses neuroimaging and genetics to assess the impact of genetic variation on brain structure and function (17). It aims to unravel the genes at risk for psychiatric disorders and to characterize the neural systems and brain functions implicated as a result of the disorders. The ability to quickly assess large numbers of subjects with easy set up of apparatus allows optical topography to be used in this emerging field. For instance, Takizawa et al. demonstrated that the prefrontal NIRS signals was able to detect the impact of catechol-*O*-methyl transferase (COMT) polymorphism in patients with schizophrenia, with the Met carriers having greater oxygenation increase in VFT than Val/Val individuals (18).

There has also been increasing debate over the potential of NIRS in diagnosis of mental illnesses. In 2004, Suto et al. reported unique disorder-specific cerebral oxygenation patterns

in depression and schizophrenia as compared to healthy controls (19). In 2013, Takizawa et al. in a multisite study further revealed frontal hemodynamic patterns in NIRS that were able to accurately distinguish among patients with major depressive disorder, schizophrenia, and bipolar disorder using specific algorithms (6). In view of such findings, the Japanese Health Ministry in 2014 approved optical topography as an "advanced medical technology" and is an insurance-covered investigation to aid differential diagnosis of depressive state (20). While many would concur that NIRS does hold potential in the area of assisted diagnosis, there are still many areas of considerations such as the need for more targeted activation paradigms to delineate the disease-specific hemodynamic changes, need for validated markers with increased diagnostic specificity, the technical and methodical difficulties involved in interpreting the data, and medico-legal implications. Thus, at its current state, it is improbable to replace conventional history taking and neuropsychological assessment in the management of psychiatric disorders.

A WINDOW INTO THE MIND–BRAIN INTERFACE

Optical topography indeed is a welcoming addition to the repertoire of brain imaging modalities, and it offers new possibilities to relook at the underlying brain mechanisms of our psychiatric patients in a more natural setting and with creative combinations of various technologies to facilitate the holistic understanding of the mind–brain interface. Most psychiatric studies using NIRS so far have concentrated on assessing prefrontal activation by using VFT, which is the most popular paradigm that is simple to administer and able to reliably show differences between patients and controls. Nevertheless, it only covers a restricted aspect of executive functioning, which would be inadequate in delineating and differentiating complex psychiatric disorders. Thus, more specific activation paradigms will need to be created to target the different groups of psychiatric conditions with their unique characteristics, and extending to various cortical areas to enhance the detection of etiologically relevant cerebral hemodynamic changes that reflect functional alteration. Although optical topography currently is still very much a research utility, with further development of this technology, it is just a matter of time before it becomes a valuable clinical tool and by then, the practice of Psychiatry would be revolutionized and demystifying of the human mind would become a reality.

AUTHOR CONTRIBUTIONS

CH wrote the manuscript; MZ and RH amended the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 01 March 2016
doi: 10.3389/fpsyt.2016.00021

DTI and Myelin Plasticity in Bipolar Disorder: Integrating Neuroimaging and Neuropathological Findings

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Bipolar disorder (BD) is a major psychiatric illness with a chronic recurrent course, ranked among the worldwide leading disabling diseases. Its pathophysiology is still not completely understood and findings are still inconclusive, though a great interest on the topic has been constantly raised by magnetic resonance imaging, genetic and neuropathological studies. In recent years, diffusion tensor imaging (DTI) investigations have prompted interest in the key role of white matter (WM) abnormalities in BD. In this report, we summarize and comment recent findings from DTI studies in BD, reporting fractional anisotropy as putative measure of WM integrity, as well as recent data from neuropathological studies focusing on oligodendrocyte involvement in WM alterations in BD. DTI research indicates that BD is most commonly associated with a WM disruption within the fronto-limbic network, which may be accompanied by other WM changes spread throughout temporal and parietal regions. Neuropathological studies, mainly focused on the fronto-limbic network, have repeatedly shown a loss in cortical and subcortical oligodendrocyte cell count, although an increased subcortical oligodendrocyte density has been also documented suggesting a putative role in remyelination processes for oligodendrocytes in BD. According to our review, a greater integration between DTI and morphological findings is needed in order to elucidate processes affecting WM, either glial loss or myelin plasticity, on the basis of a more targeted research in BD.

Keywords: bipolar disorder, diffusion tensor imaging, myelin plasticity, oligodendrocyte, white matter disruption, connectivity

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *04 December 2015*
Accepted: *09 February 2016*
Published: *01 March 2016*

Citation:
Bellani M, Boschello F, Delvecchio G, Dusi N, Altamura CA, Ruggeri M and Brambilla P (2016) DTI and Myelin Plasticity in Bipolar Disorder: Integrating Neuroimaging and Neuropathological Findings. Front. Psychiatry 7:21. doi: 10.3389/fpsyt.2016.00021

INTRODUCTION

Bipolar disorder (BD) is a major psychiatric illness that affects 1% of the population and has its onset during adolescence or early adulthood (1, 2). It significantly decreases the quality of life of patients and caregivers and increases the burden of health and social care services (3).

Since 90s, a growing interest on the neurobiological underpinnings of BD has been object of several magnetic resonance imaging (MRI) studies that, so far, have repeatedly reported diffuse white matter

Abbreviations: ACC, anterior cingulate cortex; CC, corpus callosum; DLPFC, dorsolateral prefrontal cortex; GSK3β, glycogen synthase kinase 3beta; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; OD, oligodendrocyte density; OFC, orbitofrontal cortex; PFC, prefrontal cortex; sgACC, subgenual Anterior Cingulate Cortex; SLF, superior longitudinal fasciculus.

(WM) hyperintensities at T2-weighted sequences, spread out over subcortical, periventricular and callosal WM (4, 5). BD patients are 2.5 times more likely than healthy controls and 2 times more likely than depressed patients to show these neurobiological profiles, which have been therefore considered as a putative biological correlate of BD (5–7). Pieces of evidence suggested an association between more severe WM hyperintensities and poorer outcome measures, such as increased clinical severity (8), greater number of hospitalizations, poorer response to treatments (9) and higher suicide risk (10). Nevertheless, similar patterns of WM alterations did not seem to be specific to BD, as they have been found in neuropathological processes, such as cerebrovascular damage, astrocytic gliosis and demyelination processes (6).

A weakness of structural MRI in studying WM is the limited contrast detection in WM tracts, while diffusion tensor imaging (DTI) is uniquely sensitive to WM microstructure analysis including axonal coherence, fiber density and myelin integity (11, 12). Since 2000s WM abnormalities in BD have been investigated using this imaging technique, which consists of a specific extension of MRI technology and allows a more precise identification of subtle WM derangements (13–15). Basically, DTI applies two indices for the study of WM's physical integrity: the fractional anisotropy (FA) and the apparent diffusion coefficient (ADC). FA measures the anisotropic diffusion of water molecules and ranges between 0 and 1. When water molecules diffuse along the neural fibers on their longitudinal axes, due to their directional movement constraint by thick myelin sheaths, FA is 1, whereas when water molecules diffuse toward random directions, following their Brownian motion, FA is 0. ADC is an index of the rate of water diffusion in cerebral tissues: higher values of ADC indicate less restricted diffusion; conversely, lower values of ADC point to the presence of organized fibers impeding water diffusion (16). To date, overall DTI findings in BD have reported either lower, higher or no difference in FA between patients and healthy controls (12, 15, 17). Inconsistency across findings is supposed to reflect differences among DTI studies in data acquisition protocols as well as in patient characteristics (18). Most studies involve heterogeneous samples of BD patients combining subjects in different mood states (19), which could have different neural network activation correlates (20) and different WM DTI patterns (18, 21). Moreover, BD patients' samples may differ for medication status (22), which could be considered as a relevant variable for interpreting findings. Indeed, lithium seems to act as a promyelinating factor (23, 24), whereas first and second generation antipsychotics are likely to impact on WM integrity, despite their effects vary markedly across studies ranging from promyelinating actions (24, 25) to impaired WM integrity (26).

The disruption of neural connectivity due to myelin sheath's degradation, whose etiology is not yet fully understood, is supposed to play a compelling role in the neurobiology of BD (7, 27). The molecular and cellular correlates of these structural MR and DTI findings have not been completely explained yet, although the role of glial cells has been implicated in the disruption of neural connectivity (28). In the human brain tissue, glial cells include oligodendrocytes (35%), oligodendrocytes progenitor cells (OPCs) (5%), astrocytes (45%) and microglia (5%) (24). A great amount of oligodendrocytes arise from the differentiation of OPCs till the early postnatal period, yet to a lesser extent OPCs persist in generating oligodendrocytes during adulthood (29). Adult born oligodendrocytes might be involved in *de novo* myelination of previously naked or not completed myelinated axons, as well as in myelin remodeling that allows changes in existing myelin membrane sheaths in the central nervous system (CNS) (30, 31). Many DTI studies, genome wide association studies and postmortem studies have demonstrated that BD patients showed a reduction in myelin content in the CNS, especially in subcortical regions, along with aberrant expression of myelin-related genes and a reduction in oligodendrocyte cells' count (32–34). These findings are pointing to the role of glial cells' abnormalities in the disruption of WM connectivity in BD. However, a clear correlation between WM alterations in DTI studies and changes in glial cells' population in neuropathological studies is still lacking.

In this review, we address the issue of WM alterations in BD, based on the data from the most recent DTI studies, and we focus on oligodendrocyte involvement in WM alterations in BD, emphasizing the role of myelin plasticity on the basis of the available lines of evidence.

MATERIALS AND METHODS

We carried out a literature search of published studies on the following databases: National Centre for Biotechnology Information (NCBI) PubMed (MEDLINE) and Google Scholar. We took into account published papers from August 2009 to August 2015 focusing on the following key words: bipolar disorder, diffusion tensor imaging, white matter, myelin plasticity and oligodendrocytes. The reference lists of the included studies were then searched for additional studies.

Firstly, we only considered studies published in English with a patient population of 18–65 years old affected by BD, according to DSM-IV or ICD-10 criteria, where a DTI scan was performed. We limited our analysis to FA values, as other measures of diffusivity, while potentially informative about WM impairments, were inconsistently applied across DTI studies. We included DTI studies applying either a region of interest (ROI)-based analysis or a whole brain analysis. Among whole brain DTI studies we used only voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) analysis, excluding DTI tractography studies given that methodological issues are deemed to undermine a direct comparison between tractography and VBA approaches (35). Indeed, VBA images are smoothed and statistical thresholds are applied to generate a statistical map, where differences of voxel-wise mean values between groups are shown at a local level in brain regions, instead of tractography where DTI metric values are averaged along a 3-D ROI and local differences in specific regions of the reconstructed tract could be lost (35).The search of the literature revealed 88 publications suitable for the inclusion in the present paper, of these 13 were literature reviews and 2 were meta-analyses (see **Table 1**).

Secondly, we focused on studies published in English with a patient population of 18–65 years old affected by BD, according to DSM-IV or ICD-10 criteria, where the oligodendrocyte

TABLE 1 | Reviews and meta-analyses of diffusion tensor imaging studies investigating WM in patients with bipolar disorder.

Reference	Metodology	Subjects	Main findings in BD patients
Teipel et al. (36)	Review of ROI studies and VBA studies	–	↓ FA in fronto-occipital and callosal connections, SLF, UF. ↓ FA right-sided in WM close to the PHG and sgACC
Dell'Osso et al. (37)	Review of ROI studies and VBA studies	–	↓ FA in WM of FC and OC, cingulum bundle, CC, internal capsule and FOF. ↓ FA right-sided in WM close to the PHG and sgACC. ↓ FA in ACR. ↑ FA in corticopontine/corticospinal tracts, SLF, TR
Marlinge et al. (38)	Review of ROI studies and VBA studies	–	↓ FA in CC, ACR, internal capsule and FOF. ↓ FA in WM close to right PHG (SLF, IFOF, ILF, PTR) and in WM close to right sgACC and right ACC
Hahn et al. (3)	Review of ROI studies and VBA studies	271 BD pts vs. 108 HC	↓ FA in CC ventral part in late-life BD. No studies on WM alterations in late-onset BD
Shizukuishi et al. (39)	Review of ROI studies and TBSS studies	–	↓ FA in PF WM and ↑ FA in the genu of CC. ↑ FA in left UF and ↓ FA in right UF
Nortje et al. (40)	Review and meta-analysis of VBA studies and TBSS studies	252 BD pts vs. 256 HC	↓ FA in a right posterior tempo-parietal WM cluster and in two left cingulate WM clusters
Hafeman et al. (41)	Review of ROI studies and VBA studies	430 BD pts vs. 402 HC	↓ FA (especially in depressed patients) in CC, UF, SLF, anterior TR, ACB. Medicated BD pts more similar to HC than their unmedicated counterparts
Vederine et al. (42)	Review and meta-analysis of VBA studies	289 BD pts vs. 279 HC	↓ FA in a WM cluster close to right PHG (SLF, IFOF, ILF, posterior TR) and a WM cluster close right ACC and right sgACC
Bellani and Brambilla (18)	Review of ROI studies, VBA studies, TBSS studies	429 BD pts vs. 436 HC	↓ FA in SLF, FOF and CC
Mahon et al. (43)	Review of ROI studies, VBA studies, TBSS studies	524 BD pts vs. 561 HC	↓ FA along the UF and other WM tracts subserving both the OFC and the ACC as well as in TR fibers and SLF
Heng et al. (15)	Review of ROI studies, VBA studies, TBSS studies	465 BD pts vs. 480 HC	↓ FA in PF WM. ↓ FA in projection, associative and commissural WM fibers
Palaniyappan et al. (44)	Review of ROI studies, VBA studies, TBSS studies	–	↓ FA in PF WM, ACB, temporal WM. ↑ FA in genu of CC. ↓ FA in UF, ACR, cingulate–amygdala–hippocampal connections
Agarwal et al. (6)	Review of ROI studies and VBA studies	–	↓ FA in PF WM, CC and internal capsule

BD, bipolar disorder; WM, white matter; HC, healthy controls; DTI, diffusion tensor imaging; ROI, region of interest; VBA, voxel-based analysis; TBSS, tract-based spatial statistics; FA, fractional anisotropy; pts, patients; CC, corpus callosum; SLF, superior longitudinal fasciculus; UF, uncinated fasciculus; PHG, parahippocampal gyrus; sgACC, subgenual Anterior Cingulate Cortex; ACC, anterior cingulate cortex; FC, frontal cortex; OC, occipital cortex; FOF, fronto-occipital fasciculus; ACR, anterior corona radiata, TR, thalamic radiation; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PTR, posterior thalamic radiation; PF, prefrontal; OFC, orbitofrontal cortex; OF, orbitofrontal; ACR, anterior corona radiata, ACB, anterior cingulum bundle.

involvement was specifically addressed at a neuropathological level. We included studies focused on perineuronal and myelinating oligodendrocytes because oligodendrocytes exist both in GM and WM and alterations in GM glial organization are thought to be related to WM changes (43). We excluded and considered unfocused all the studies investigating glial cells without considering oligodendrocyte density (OD) in BD patients and controls. Eight studies identified by the literature search were judged to fulfill these inclusion criteria (see **Table 2**).

RESULTS AND DISCUSSION

Several structural MRI studies, using both ROI analysis and VBA, indicated that WM hyperintensities, especially in the prefrontal and frontal WM, were associated with BD compared with healthy controls (4, 43). These WM abnormalities' observations have been replicated in studies on first-episode BD patients (51) and adolescents with BD (52, 53). All together, these studies suggested that, besides confounders as brain aging and medical illnesses, other processes should be involved in the pathophysiology of BD.

Diffusion tensor imaging provides a more sensitive tool, compared to structural MRI, to investigate WM integrity and microstructure (11, 12). In the following paragraphs, DTI studies accordingly to the different methodological approaches – ROI analysis, VBA and TBSS analysis – will be briefly debated.

ROI-Based Analysis

Most of DTI studies based on ROI approach showed lower FA among BD patients compared with healthy controls, mainly in WM tracts in prefrontal areas, anterior cingulum, callosal areas, and limbic-striatal areas (54–56). These abnormalities, particularly in deep prefrontal WM, have been reported since the first episode of mania (14). In support of these findings, a review of ROI-based studies has recently confirmed a loss of bundle coherence and alignment of WM fibers in the following areas in BD: deep WM in frontal and occipital lobes, anterior cingulum, corpus callosum (CC), anterior corona radiata and internal capsule (38).

TABLE 2 | Neuropathological postmortem studies focusing on oligodendrocyte involvement in bipolar disorder.

Reference	Methodology	Subjects	Age, years (mean ± SD)	Sex ratio M/F	Main findings
Hercher et al. (28)	Neuropathological postmortem assessment of DLPC WM in SZ, BD, and HC (2-D cell counting technique)	20 SZ vs. 20 BD vs. 20 HC	SZ 44.7 (±6.9), BD 47.4 (±0.7), HC 45 (±6.5)	SZ 13/7, BD 8/12, HC 14/6	↑ OD in BD vs. HC. No differences in SZ vs. HC. No differences in AD among the groups just a trend toward ↓ AD in SZ vs. HC
Savitz et al. (45)	Review of postmortem studies on mPFC neuronal density and glial cell density in BD and HC	–	–	–	3-D cell counting studies:↓ glial cell density (predominantly ↓ OD) in BD vs. HC. Unclear if ↓ ND in BD vs. HC
Haroutunian et al. (46)	Review of postmortem studies and genetic studies on myelin and oligodendrocyte involvement in SZ, BD, and MDD	–	–	–	↓ cortical OD and myelin gene disruption in SZ, BD and MDD vs. HC. ↓ subcortical OD in BD and MDD vs. SZ
Williams et al. (47)	Neuropathological postmortem assessment in sgACC and genu of CC among SZ, BD, MDD, and HC (2-D cell counting technique)	10 SZ vs. 15 BD vs. 20 MDD vs. 19 HC	SZ 65.5 (±2.3), BD 56.1 (±5.2), MDD 47.6 (±3.1), HC 65.5 (±2.3)	SZ 5/5, BD 6/9, MDD 7/13, HC 11/8	↓ AD in sgACC and anterior CC WM in SZ vs. HC. No changes in OD among different groups in sgACC and anterior CC WM
Gos et al. (48)	Neuropathological postmortem assessment of AD and OD in HPC (alveus and CA1 pyramidal layer) among MDD, BD, and HC (2-D cell counting technique)	6 BD vs. 9 MDD vs. 13 HC	BD 55.7 (±13.3), MDD 49.6 (±11), HC 55.3 (±12.3)	BD 3/3, MDD 2/7, HC 7/5	Bilateral ↓ AD in CA1 pyramidal layer in MDD and BD vs. HC. ↓ OD in left alveus only in BD vs. HC
Hayashi et al. (49)	Neuropathological postmortem assessment of PFC and ITC GM to examine OD among SZ, BD, and HC (3-D cell counting technique)	10 PFC SZ vs. 12 PFC BD vs. 12 PFC HC 11 ITC SZ vs. 11 ITC BD vs. 11 ITC HC	PFC SZ 43 (±14), BD 41 (±11), HC 48 (±11) ITC SZ 45 (±14), BD 41 (±12), HC 50 (±10)	PFC: SZ 7/3, BD 7/5, HC 8/4 ITC: SZ 6/5, BD 6/5, HC 7/5	↓ OD in PFC GM of BD vs. SZ and HC. ↓ ID in ITC GM of BD and SZ vs. HC
Mahon et al. (43)	Review of postmortem neuroimaging and genetic studies on WM in BD	–	–	–	3-D cell counting studies: ↓ cortical OD in sgACC and DLPC in BD vs. HC. Disruption in myelin and oligodendrocyte-related genes expression in BD
Vostrikov et al. (50)	Neuropathological postmortem assessment of OD related to age in PFC among SZ, MDD, BD, and HC (2-D cell counting technique)	15 SZ vs. 15 BD vs. 15 MDD vs. 15 HC	SZ 44.5 (±13.1), BD 42.3 (±11.7), MDD 46.5 (±9.3), HC 48.1 (±10.7)	SZ 9/6, BD 9/6, MDD 9/6, HC 9/6	↓ OD in young BD vs. HC. Age-related ↑ OD in HC, but not in SZ, MDD, and BD

SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; HC, healthy controls; pts, patients; GM, gray matter; WM, white matter; DLPFC, dorso lateral prefrontal cortex; OD, oligodencrocyte density; ID, interneuron density; AD, astrocyte density; ND, neuronal density; sgACC, subgenual Anterior Cingulate Cortex; CC, corpus callosum; HPC, hippocampus; ITC, inferior temporal cortex.

Though consistent and replicated, these results might be limited by a selection bias, as ROI-based approach is hypothesis-driven and provides information only about selected brain regions.

Voxel-Based Analysis

Voxel-based analysis allows DTI data analysis over the whole brain volume without *a priori* hypotheses on specific regions of interest, thus overcoming possible selection bias from the ROI approach.

The current findings from VBA-DTI studies suggest the existence of diffuse WM microstructural abnormalities as BD's trait feature, raising the intriguing notion of a disconnected framework within fronto-limbic areas as well as between fronto-limbic and temporal, parietal and occipital lobes. A recent meta-analysis (40) showed decreased FA in all major classes of WM tracts (i.e., commissural, association and projection), with more robust findings on Bipolar Type 1 vs. Bipolar Type 2 patients. VBA data displayed significant clusters of decreased FA within right temporo-parietal WM, involving both inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF), left cingulum and left anterior cingulate. These findings suggest a wide alteration in the WM of CNS in BD, which involves not only an anterior fronto-limbic pathway but also fibers connecting temporal and parietal cortices. Consistent with these observations, a recent integrated structural MRI/DTI study (57) found a global reduction of WM volume and WM clusters of decreased FA in BD patients, ranging from prefrontal WM to the splenium of CC and posterior cingulum bundle. Additionally, the authors also investigated whether pharmacological treatment could have influenced their findings and they observed no significant association between lithium medication and any DTI measures, while total GM volume was increased with significant clusters in temporal lobes in patients treated with lithium. Moreover, a meta-analysis of VBA-DTI studies in BD (38) found two consistent clusters of FA and mean diffusivity alterations both of them located in areas relevant for emotional processing in

the right hemisphere. The first cluster was close to the right parahippocampal gyrus in a WM area crossed by the superior longitudinal fasciculus (SLF), ILF, IFOF and posterior thalamic radiations, while the second one was close to the right anterior cingulate cortex (ACC) and the right subgenual cingulate cortex (sgACC). These findings prompted the authors to speculate that a pattern of disrupted WM connectivity may underlie the abnormal emotional processing in BD patients compared with healthy controls. It is worth highlighting that a disruption of SLF might contribute to fronto-temporal disconnection, which could be relevant to emotional cognitive modulation and inhibition, whereas the disruption of ILF and IFOF could underlie facial emotion recognition deficits, proposed as a potential endophenotype for BD (58, 59). Furthermore, both ACC and sgACC are thought to be involved in identification of emotionally salient stimuli and WM diffusion abnormalities, clustered close to these areas, have been associated with dysfunctional emotional processes in BD (60). Indeed, a disrupted WM connectivity between these regions and a dorsal cognitive network [dorsolateral prefrontal cortex (DLPFC), dorsal cingulate cortex, precuneus, cuneus] is supposed to play a role in over reactivity of ACC and sgACC during emotional processing in bipolar patients (61).

White matter microstructure changes have been also regarded as a possible DTI endophenotypic marker in BD. Interestingly, a VBA-DTI study comparing individuals with BD, their ultra-risk (UR) relatives and healthy controls found no significant FA differences in UR vs. healthy controls (62). However, the *post hoc* analysis, including the density of illness within families, revealed a reduction in FA associated with increasing genetic liability in prefrontal WM, SLF, CC and uncinate fasciculus. Furthermore, a lower FA in SLF has been reported in children at risk of BD in a study comparing children at risk of BD with a sample of unaffected children (63).

Eventually, the notion of early WM markers of vulnerability for BD has been recently strengthened by a review of DTI studies in BD children and adolescents (2). In keeping with VBA-DTI findings in adults with BD, the study reported that BD children and adolescents showed a pattern of decreased FA both in fronto-temporal intrahemispheric WM (prefrontal WM, cingulum bundle, WM bundles to dorsal frontal regions, basal ganglia, thalamus and posterior association cortices) and fronto-temporal interhemispheric WM (anterior CC).

Tract-Based Spatial Statistics Analysis

Tract-based spatial statistics analysis is a whole brain analysis of DTI data, which focuses on the centers of all fiber bundles, improving the probability that the given space voxels contain uniform data from the same WM tract (the most compact WM skeleton). TBSS approach overcomes the misinterpretation of crossing fibers areas hindering the reliability of traditional voxel-wise analysis (64).

Significant widespread decreases in FA have been predominantly reported so far by TBSS DTI studies among BD patients compared with healthy controls with WM changes encompassing all major WM tracts (projection, association, callosal and limbic fibers). Indeed, in a recent published meta-analysis of TBSS studies, Nortje and colleagues (40) showed a decreased FA in all main classes of WM tracts, though the pattern of mostly involved bundles was different among independent studies. Consistent with these results, a TBSS study, employing a group of bipolar I and II patients in comparison with a group of healthy controls, reported in BD patients a significant lower FA in CC, cingulum bundles, fornices, SLF, ILF, fronto-occipital fasciculus, thalamic radiation and uncinate fasciculus (65). These widespread WM diffusion abnormalities, including fronto-temporal and ventral striatal regions, were marked by significant differences in diffusivity measures other than FA, leading the authors to conclude that dysmyelination and demyelination rather than axonal loss are implicated in BD (66, 67). Providing further support to these lines of evidence, a TBSS study considering 40 inpatients with bipolar depression vs. 21 healthy controls showed a reduced FA in the following WM areas: CC, cingulum, corona radiata and SLF (68). The authors considered the disrupted connectivity evidenced in interhemispheric connections as well as in frontal, parietal and fronto-occipital connections as the biological underpinning of cognitive and emotional deficits of bipolar depression. Notably, in this study, lower FA values were coupled with higher radial diffusivity and mean diffusivity with no differences in parallel diffusivity, consistently with those findings showing a disruption in myelin sheaths without axonal loss (69).

Finally, DTI measures have been also investigated as biomarkers of treatment response, even though robust evidence on this subject is still missing with studies focusing mostly on major depressive disorder (70, 71). To the best of our knowledge, the role of WM microstructure in predicting treatment efficacy in BD has been investigated in just one TBSS DTI study (72). Authors revealed a significant association between poor response to chronotherapeutic treatment in bipolar depression and increased radial diffusivity and mean diffusivity in WM tracts involved in cognitive and emotional deficits (CC, cingulum bundle, IFOF, SLF, corona radiata and anterior thalamic radiation).

Unfortunately, DTI measures, regardless of which approach is applied, are relatively non-specific and do not clearly differentiate between axon and myelin-based abnormalities (73). As outlined in a recently published study (74), DTI quantifies diffusion of water molecules and water exists in both intracellular and extracellular spaces (with exchange between two). Thus, the authors applied a more refined MRI approach, using magnetization transfer ratio, in order to study myelin content, and diffusion tensor spectroscopy, in order to study *N*-acetylaspartate diffusion within axons. Their results showed reduced myelin content but no changes in intra-axonal geometry, considered as a proxy of axonal integrity, in patients with BD vs. healthy controls. Furthermore, axonal demyelination is just one of several possible factors impacting on FA values, including bundle coherence, crossing fibers, water concentration and neuronal loss (13). Therefore, findings of abnormal FA in either direction that are not supported or followed up by neuropathological postmortem investigations should be interpreted with caution (43).

Myelin Plasticity

In humans, developmental myelination is a long-lasting process continuing at least until the fourth decade of life (75, 76) and

proceeding in predictable spatial and temporal patterns (i.e., thicker axons are myelinated before thinner axons, brain regions devoted to more basic and homeostatic functions, such as brainstem, are myelinated before high level integrative areas, such as cortical association fibers) (77). During and even after the developmental myelination, mammalian CNS myelin has shown to be plastic and sensitive to experience dependent structural changes: this feature is referred to as myelin plasticity (78).

So far, postmortem studies of individuals with BD have shown sparse and contradictory findings about WM and GM changes in number, size and density of different glial cell populations (43, 46, 49). As regards the oligodendrocytes involvement, evidence from several morphometric postmortem studies, identified in our literature search, pointed out that BD patients might be affected by an oligodendrocyte cell loss in the same areas where DTI studies have reported WM diffusivity abnormalities. Indeed, lending support to this speculation, a review of postmortem neuropathological studies, focusing on medial prefrontal cortex (mPFC) network in BD patients, has recently reported a reduction in glial cells both in sgACC and DLPFC (45). Both perineuronal and myelinating oligodendroglia cells were the most clearly involved glial cell populations. Interestingly, the oligodendroglia cell loss in BD was correlated with a putative increase of neuronal density in sgACC, orbitofrontal cortex (OFC) and DLPFC due to dendritic atrophy (the great amount of GM consisting of neuropil). Furthermore, a neuropathological study (48) evaluating astro and oligodendroglial expression of SB100 (a glial marker protein), in CA1 pyramidal layer and the alveus of hippocampus, showed a decreased OD in BD compared with healthy controls in the left alveus. Congruent with these neuropathological observations, many genetic studies, which support the role of oligodendrocyte dysfunction in BD, reported a downregulation of key oligodendrocyte and myelination genes in BD compared with healthy controls (20, 24, 79, 80). Notably, Tkachev and colleagues (81) provided a strong evidence for a downregulation of key oligodendrocyte and myelination genes, including transcription factors that regulate these genes, in bipolar and schizophrenic patients compared with healthy controls, by using quantitative polymerase chain reaction and microarray analysis. A selective reduction in oligodendrocyte-related gene expression was noted, after controlling for confounding variables such as medication and alcohol abuse, pointing toward a cellular dysfunction or death. Even if there are not conclusive evidences, the mechanism underlying an oligodendroglia cell loss is likely to affect inhibitory GABAergic transmission: a GABAergic interneuron loss, which decreases the inhibitory feedback on glutamatergic neurons, may lead to excitotoxicity-induced dendritic atrophy and/or oligodendrocyte cell loss (82). As known, oligodendrocytes express AMPA and kainate-type glutamate receptors, therefore they are highly sensitive to excitotoxic damage from an excessive glutamate-mediated activation (83, 84).

However, in contrast to the evidence for an oligodedroglia cell loss, a recent study investigating the morphological basis underlying WM alterations located in DLPFC in bipolar and schizophrenia patients showed an increased OD in the BD group compared both with schizophrenia and healthy control subjects (28). It is worth noting that the increased OD in the subcortical WM of DLPFC was not correlated with higher myelin content, as evidenced by the increase of a marker protein located in oligodendrocyte cell bodies (2′3′ cyclic 3′phosphodiesterase) and no changes in a marker protein located in compact myelin (myelin basic protein). These findings are very intriguing as, along with the observation of an increased myelin peroxidation in the myelin fraction in BD patients (85), they strengthen the hypothesis that an increased OD could reflect a compensatory mechanism of repairing damage. In this perspective, the proliferation and differentiation of OPCs into mature oligodendrocytes could play a role in replacing damaged myelin throughout a remyelination process in the adult brain. With regard to the putative compensatory mechanism to restore damaged myelin, Bartzokis (24) has mainly shifted the emphasis from subcortical into intracortical myelination processes as key factor in better understanding BD's pathophysiology. In the human brain development, during childhood the subcortical WM myelination would achieve a network of axons' synchronization, connecting widely distributed brain regions, whereas throughout adulthood the intracortical myelination would make faster and more synchronized this transmission, by adding further myelin sheath. Intracortical myelin could compensate for a disruption in transmission along WM subcortical fibers, due to either subcortical myelin damages or subcortical remyelination processes which produce thinner myelin sheaths. These events could influence the quality of neurotransmission as the thickness of myelin sheaths is inversely correlated with speed of conduction and network synchronization (19). If an adequate intracortical myelin plasticity may initially compensate for subcortical transmission delays, during the course of the illness an increasing intracortical myelin disruption could undermine this compensation mechanism and thus give raise to an increasingly disrupted WM connectivity (24). At the onset of BD, subcortical myelin deficits seem to be more prominent than intracortical myelin deficits (86) but, during the course of the illness, significant intracortical oligodendrocyte deficits develop in BD (50) while cognitive deficits worsen (87, 88). Noteworthily, converging evidence of a decreased OD in the gray matter of DLFC and sgACC in BD, as compared to healthy controls, has been raised by several reviews of morphometric studies (43, 45), though not homogeneous in terms of cell counting technique applied (either 2-dimensional or 3-dimensional). Furthermore, a study (49) applying a 3-dimensional cell counting method confirmed the existence of a significantly decreased intracortical OD in the PFC of BD patients as compared not only to healthy controls but also to SZ patients, thus suggesting this neuropathological abnormality as more commonly associated to BD than SZ. Eventually, it is of interest to mention that another study (50) reported a reduction of OD in PFC of BD patients along with a loss of age-related increase in OD of either BD or SZ or MDD patients in layer VI of the PFC (BA 9) as compared to controls. These findings led the authors to postulate that common age-related process of OD increase is dysregulated in SZ and mood disorders. Taken together, these findings are consistent with a oligodendrocyte cell loss affecting the intracortical myelination

within the fronto-limbic network in BD, whereas direct evidence from human neuropathological studies for the role of myelin plasticity in BD is still missing.

It should be noted that neuropathological results regarding WM alterations in BD are limited by several key factors listed/described as follows (89, 90): they are prominently focused on prefrontal WM and show heterogeneous and quite inconsistent findings; there are wide discrepancies between the 2-D vs. 3-D counting methods, given that caution must be taken particularly with 2-D counting methods, which have a higher risk of sampling bias than methods which involve a stereological approach (91); many histological variables can bias the results impacting on postmortem tissue such as longer fixation time, increased pH and post-mortem interval; psychiatric medication, non-prescription drugs and substance abuse (especially alcohol abuse) should be taken into account as possible confounding factors, especially because the lifetime exposure can alter brain biology. As far as psychotropic treatment in BD is concerned, both mood stabilizers and antipsychotics may drive promyelinating effects working on the inhibition of glycogen synthase kinase 3beta (GSK3β) throughout different biochemical pathways (38, 46). Lithium seems to mainly target subcortical WM throughout the GSK3β inhibition both directly via competition with magnesium and indirectly by increasing serine-phorphorylation of GSK3 through AKT (a serine/threonine kinase) activation (92), whereas first and second generation antipsychotics have been reported to promote predominantly intracortical myelination by inhibiting GSK3 signaling via dopamine 2 receptor blockade and 5HT2A receptor blockade (93).

Finally, oligodendrocyte alterations are not limited to BD but encompass most psychiatric conditions including major depression disorder, schizophrenia, attention-deficit and hyperactivity disorder and Alzheimer's disease (94). The essential mechanism underling these alterations remains partially unknown; however, most of the current models point to a stress-related vulnerability mechanism prompted by disturbances in chromatin regulation, glutamate-mediated excitoxicity and glucocorticoid mechanism (95): a deficit/dysfunction in oligodendrocytes population could disrupt WM connectivity, affecting the trophic axonal support and thus determining a suboptimal conduction of action potentials.

CONCLUSION

So far, DTI studies have consistently shown an alteration in prefrontal–limbic anatomical connectivity, leading to the hypothesis of BD as a connectivity disorder. Accordingly to this hypothesis, prefrontal regions would fail to regulate limbic regions, triggering emotional hyper reactivity and emotional instability. Besides this core and more consistent feature, rising lines of evidence are considering temporo-parietal WM abnormalities of long association tracts as a structural background of cognitive rather than affective symptoms in BD.

Although DTI studies provided compelling findings, some inaccuracies remain in the current DTI technique (18, 40, 68): clusters of WM alterations do not delineate tidily and WM tracts have an interindividual variability making it unclear which tracts are involved; WM microstructure may be affected by age, substance use, lithium use, antipsychotic use and genetic loading for BD; eventually, there are often differences among study populations with regard to bipolar subtype, affective state, duration of illness, medication status, comorbidities and family history.

Furthermore, morphological studies with larger and more homogeneous samples are required to clarify oligodendrocytes dysfunctions as well as to investigate the possible role of cortical and subcortical myelin plasticity in BD. In this regard, postmortem studies should have a key role to refine DTI studies' results. Indeed, it should be clearly kept in mind that any inference on tissue microstructure arising from DTI data is based on an indirect measurement "prior to making bold claims about white matter integrity" (96).

AUTHOR CONTRIBUTIONS

MB and PB were responsible for conceptual design, manuscript, and table revision. FB was responsible for manuscript and table generation. ND and GV were responsible for main manuscript revisions. CA and MR were involved in the revision process.

FUNDING

This study was partially supported by grants from the Italian Ministry of Health RF-2011-02352308 (PB), GR-2010-2319022 (MB).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

MINI REVIEW
published: 19 April 2016
doi: 10.3389/fpsyt.2016.00061

GABA System in Schizophrenia and Mood Disorders: A Mini Review on Third-Generation Imaging Studies

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Third-generation neuroimaging research has been enriched by advances in magnetic resonance spectroscopy (MRS) measuring the concentration of important neurotransmitters, such as the inhibitory amino acid GABA. Here, we performed a systematic mini-review on brain MRS studies measuring GABA concentration in patients affected by schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). We wondered whether multimodal investigations could overcome intrinsic technical limits of MRS giving a broader view of mental disorders pathogenesis. In SZ, unimodal studies gave mixed results, as increased, decreased, or unaltered GABA levels were reported depending on region, disease phase, and treatment. Conversely, multimodal results showed reduced level of glutamate, but not of GABA, in patients mirrored by *in vitro* biochemical findings revealing hippocampal reduction in glutamate signaling in SZ, and no deficits in GABA synthesis. Moreover, a mouse model confirmed the unique pathological characteristic of glutamate function in SZ. Unimodal studies in BD revealed again, inconsistent results, while no multimodal investigations including MRS on GABA exist. In MDD, unimodal studies could not differentiate patients from controls nor characterize high-risk subjects and remitted patients. However, a multimodal study combining functional magnetic resonance imaging and MRS revealed that cingulate cortex activity is related to glutamate, *N*-acetylaspartate levels and anhedonia in patients, and to GABA concentration in healthy subjects, improving the distinction between MDD and physiology. Overall, our results show that unimodal studies do not indicate GABA as a biomarker for the psychiatric disorders considered. Conversely, multimodal studies can widen the understanding of the link between psychopathology, genetics, neuroanatomy, and functional–biochemical brain activity in mental disorders. Although scarce, multimodal approaches seem promising for moving from GABA MRS unimodal-descriptive to causal level, and for integrating GABA results into a more comprehensive interpretation of mental disorder pathophysiology.

Keywords: GABA, MRS, multimodal imaging, schizophrenia, bipolar disorder, major depressive disorder

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Gabriele Sani, Sapienza University of Rome, Italy
Agata Szulc, Medical University of Warsaw, Poland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *22 December 2015*
Accepted: *29 March 2016*
Published: *19 April 2016*

Citation:
Chiapponi C, Piras F, Piras F, Caltagirone C and Spalletta G (2016) GABA System in Schizophrenia and Mood Disorders: A Mini Review on Third-Generation Imaging Studies. Front. Psychiatry 7:61. doi: 10.3389/fpsyt.2016.00061

INTRODUCTION

An imbalance between excitation and inhibition in brain neuronal transmission has been hypothesized as one of the molecular mechanisms responsible for psychiatric disorders (1–5). In this context, multimodal studies coupling the continuous technical progresses in neuroimaging to methods for measuring neurotramsitter concentrations may represent a turning point for *in vivo* evidence of postmortem (6–8) and animal model (9–12) results. Moreover, the chance to link psychopathology, genetics, neuroanatomy, and functional–biochemical brain activity may take psychiatric research to the causal understanding of patients' illness.

The support given by newly developed improvements in well known technologies, such as proton magnetic resonance spectroscopy (MRS) (13–15), has been fundamental to encourage *in vivo* research on gamma-aminobutyric acid (GABA) in brain physiology and pathology (16–18). GABA is the primary inhibitory neurotransmitter in the mammalian central nervous system. Theories on its dysfunction in schizophrenia (SZ) assume that alterations in the neural circuitry involving GABA have a role in the mechanisms of the disorder and associated cognitive deficits (19–21). The role of GABA dysfunction in different psychiatric disorders such as bipolar disorder (BD), or major depressive disorder (MDD) is also established (3, 22, 23).

Magnetic resonance spectroscopy is the election technique to non-invasively measure *in vivo* GABA concentration in selected brain regions (18, 24). However, direct interpretation of MRS results is limited by intrinsic features of the technique. In particular, acquisition of GABA signal is restricted to large (e.g., 3×3×3 cm^3) single voxels, since multi-voxel spectroscopy usually measures metabolites with longer T2 relaxation, such as *N*-acetylaspartate (NAA), choline (Cho), and creatine (Cr). This results in a broad between-studies heterogeneity in the anatomical region investigated. Moreover, MRS can only detect total concentration of neurochemicals and cannot distinguish between separate functional pools, thus impeding conclusions on neurotransmitters availability.

In this context, multimodal approaches, combining MRS with other complementary techniques, would lead to a solid and comprehensive interpretation of neurochemical underpinnings of brain pathologies. As a case in point, multimodal MRS and functional magnetic resonance imaging (fMRI) would help in depicting the neurochemical and functional pathological mechanisms responsible for complex disorders. The support from electrobiological measurements such as electroencephalography (EEG) or magnetoencephalography (MEG), measuring the oscillatory activity in brain neuronal ensembles, could be fundamental in interpreting results on GABA concentration since the latter has been shown to be positively correlated with stimulus specific neuronal oscillations (25–27). Similarly, findings from *in vitro* tissue biochemistry, animal models, and genetics could provide data at higher spatial resolution and further mechanistic insights into the interpretation of GABA concentration (28).

On the basis of these considerations, we reviewed research articles focusing on GABA as measured by MRS in SZ and mood disorders (i.e., BD and MDD). In particular, we analyzed whether studies combining different approaches could overcome the technical limits intrinsic to MRS and give a broader view of the mechanisms involved into mental disorders.

METHODS

To investigate recent MRS studies evaluating GABA level in the brain, we performed a systematic literature search on PubMed, PsycNET (including PsycINFO, PsycBOOKS, PsycCRITIQUES, PsycARTICLES, and PsycEXTRA databases), and Scopus database till November 2015 using the keywords "GABA" *AND* "spectroscopy" *AND* any of the following terms: "schizophrenia," "bipolar disorder," "major depressive disorder." The reference list of identified articles and review papers was also hand searched to obtain additional articles. Inclusion criteria for studies selection were (1) English language, (2) articles published in peer-reviewed journals after 2000, (3) original research article (comments, letters to editors and review articles were excluded), (4a) inclusion of patients diagnosed with the specific neuropsychiatric disorder of interest according to ICD or DSM criteria or (4b) inclusion of high risk (HR) subjects, (5) inclusion of at least 10 patients, (6) comparison between patients and healthy controls (HC), (7) performance of MRS using a magnetic field of at least 3 T (to have a good signal-to-noise ratio and to resolve GABA peak from those of other more concentrated molecular compounds, e.g., NAA or Cr).

In the search for SZ studies, 72 papers were initially identified. Among them, 11 were not original researches (9 reviews, 1 comment, and 1 letter), 2 studies did not consider HC and 9 did not include SZ patients, 22 papers did not include humans (e.g., studies on animal models and *in vitro* measurements), 9 studies measured the unresolved glutamate + glutamine (Glx) with GABA contamination peak as a proxy of GABA concentration, 1 study included less than 10 patients and 6 studies were published before 2000. At the end of the selection process, 12 studies on SZ fulfilled the inclusion criteria.

In the search for BD studies, 21 papers were screened, but we excluded 7 reviews, 3 studies not performing *in vivo* MRS on humans, 1 on healthy men only, 1 not measuring GABA, 3 studies considering Glx, and 1 including less than10 patients. Only five studies survived the selection process for BD.

At last, 53 studies were initially identified for MDD, but only 11 studies were eligible for the review, and 42 were excluded (6 studies without a control group, 5 not focusing on MDD patients, 6 not using *in vivo* MRS on humans, 11 reviews, 1 comment, 5 measuring Glx, 4 considering less than 10 patients, 3 not in English, and 1 published before 2000).

RESULTS

Schizophrenia

GABA MRS results in SZ are very scattered, since GABA concentration was found reduced, increased, or unaltered in patients (see **Table 1**). Such heterogeneity is mostly due to the different methodological approaches used, as studies vary in terms of patients' clinical characteristics, brain region under investigation, and aims of the studies. Indeed, while most authors evaluated the

TABLE 1 | Studies comparing GABA concentration between SZ patients and HC.

Reference	Sociodemographic characteristics				Clinical characteristics			Probed brain region	Brain region of altered GABA in patients	Additional findings	Other techniques
	Sample size		Age [mean (SD) or years range]		Illness duration [mean (SD) or years range]	GMM [no. patients (%)]	Antipsychotics [no. patients (%)]				
	Patients	HC	Patients	HC							
SZ < HC											
Rowland et al. (30)	31 older	37 older	48.3 (5.8)	51.0 (6.0)	24.0 (9.8)	Anticholinergics: 1 (3)	Typ: 4 (13); Atyp: 18 (58); Both: 6 (19); none: 3 (10)	MFC	MFC		
	29 younger	40 younger	25.7 (4.3)	25.3 (4.6)	5.6 (4.6)	Anticholinergics: 2 (7)	Typ: 1 (3); Atyp: 25 (87); Both: 1 (3); None: 2 (7)	MFC			
Rowland et al. (29)	11 younger	10 younger	30.2 (6.6)	33.4 (6.5)	7.7 (4.1)	Benzodiazepines or mood stabilizers free at scan time	Atyp: 11 (100)	ACC, CSO	ACC		
	10 older	10 older	51.1 (4.0)	49.4 (3.9)	25.5 (6.5)	Benzodiazepines or mood stabilizers free at scan time	Typ: 2 (20); Atyp: 8 (80)	ACC, CSO			
Marsman et al. (31)	17	23	27.6 (6.1)	27.7 (5.3)	6.4 (6.8)	Benzodiazepines current: 6 (35) Benzodiazepines lifetime: 11 (65)	Typ: 3 (18); Atyp: 10 (59); Both: 4 (23)	PFC, POC	PFC	GABA reduction independent from antipsychotics dosage and benzodiazepines use	
Kelemen et al. (32)	28	20	24.9 (8.3)	24.2 (6.9)	<1	T0: drug naive: 28 (100); FU: anticholinergics: 5 (18); benzodiazepines: 16 (57); mood stabilizers: 5 (18)	T0: None: 28 (100); FU: Typ: 3 (11); Atyp: 25 (89)	OC	OC	GABA_SZ_T0 = GABA_SZ_FU	
Yoon et al. (33)	13	13	27.5 (8.8)	28.1 (8.2)	Na	Na	Typ: 1 (8); Atyp: 7 (54); None: 5 (38)	OC	OC	Medication dosage did not influence results	
Goto et al. (34)	16	18	30 (11)	15–49	<0.5	Na	T0: None: 16 (100); FU: Atyp: 16 (100)	MFC, ltBG, POC	ltBG	GABA_SZ_T0 = GABA_SZ_FU	
SZ = HC											
Stan et al. (28)	18	16	41.94 (8.5)	35.63 (11.74)	Na	Anticonvulsants: 1 (5); benzodiazepines: 2 (11), valproic acid: 2 (11)	Typ, Atyp, Both: Na; None: 7 (39)	Hippocampus		Hippocampal GABA *in vivo*, *in vitro* and in animals did not differ between SZ and controls	Hippocampal dissection and tissue immunoblotting on postmortem SZ patients Animal MRS on the DG-selective GRIN1 knockout mice

(Continued)

TABLE 1 | **Continued**

Reference	Sociodemographic characteristics				Clinical characteristics			Probed brain region	Brain region of altered GABA in patients	Additional findings	Other techniques
	Sample size		Age [mean (SD) or years range]		Illness duration [mean (SD) or years range]	GMM [no. patients (%)]	Antipsychotics [no. patients (%)]				
	Patients	HC	Patients	HC							
Chen et al. (36)	12	12	31.00 (10.79)	33.08 (8.23)	Na	Na	Atyp: 9 (75); None: 3 (25)	DLPFC		Correlation between GABA levels and gamma band oscillation in SZ and HC	EEG at rest EEG during a working memory task
Tayoshi et al. (35)	38	29	34.0 (10.0)	34.0 (10.2)	11.1 (9.4)	Benzodiazepines: 16 (42)	Typ: 16 (42); Atyp: 22 (58)	ACC, ltBG		ltBG: GABA_Typ > GABA_Atyp	
SZ > HC											
De la Fuente-Sandoval et al. (39)	23 UHR	24	20.7 (4.1)	21.4 (3.3)	<1	Medication free for T >12 weeks: 23 (100)	None: 23 (100)	Dorsal caudate, MPFC	Dorsal caudate, MPFC		
Kegeles et al. (37)	16 unmed[a], 16 med	22	unmed: 32 (11), med: 32 (10)	33 (8)	unmed: 7 (7), med: 9 (8)	Benzodiazepines free at scan time: 32 (100)	med: Atyp: 16 (100)	MPFC, DLPFC	MPFC	GABA_SZ_ unmed > GABA_HC GABA_SZ_med = GABA_ HC	
Ongür et al. (38)	21	19	39.0 (10.8)	36.3 (9.8)	Na	Anticonvulsants: 6 (28); benzodiazepines: 10 (48); lithium: 4 (19)	Typ: 3 (14); Atyp: 16 (76); Both: 1 (5); None: 1 (5)	ACC, POC	ACC + POC, averaged		

[a]*Patients free of antipsychotic medication treatment for a minimum of 14 days prior to the scan.*

ACC, anterior cingulate cortex; Atyp, patients taking atypical antipsychotics; CSO, centrum semiovale region; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; FU, follow up; GMM, GABA-modulating medication; HC, healthy controls; ltBG, left basal ganglia; med, medicated; MFC, medial frontal cortex; MPFC, medial prefrontal cortex; Na, not available; OC, occipital cortex; PFC, prefrontal cortex; POC, parieto-occipital cortex; SD, standard deviation; SZ, schizophrenia patients; T, time; T0, baseline; Typ, patients taking typical antipsychotics; UHR, ultra high risk patients; unmed, unmedicated.

diagnosis effect on GABA concentration, others considered the effect of age, of antipsychotics, and the role of GABA in different illness phases.

The most reported result (i.e., replicated in six studies) is that GABA concentration is reduced in SZ patients with respect to HC (29–34). Specifically, GABA was reduced in medial frontal cortex (MFC) (29, 30) and occipital cortex (OC) (32, 33), and the result was modulated by age in MFC (29, 30) and not affected by current medication type or dosage in OC (32, 33). The observed reduction in MFC GABA level in old SZ subjects as compared to age-matched HC suggests that GABA concentration decreases as age increases in patients and not in controls (29, 30). The independence from medication dosage in the OC (33) was further extended to the basal ganglia (34) suggesting that GABA reduction in these areas is driven by the disorder, being observable also in first-episode patients (32), and not an effect of treatment. A reduced GABA level in prefrontal areas of SZ patients was described only performing MRS at very high (7 T) magnetic field (31). Conversely, three studies (34–36) failed to find alterations in GABA level in SZ with respect to HC in any of the considered regions. Among them, one study found that patients taking only typical antipsychotics had higher GABA concentration than those taking only atypical antipsychotics (35). The other two studies failing to find GABA alterations in SZ, probed the hippocampus and the dorsolateral prefrontal cortex (DLPFC) (28, 36). These studies are of particular interest since they combined MRS with different experimental techniques. In particular, one correlated GABA levels in DLPFC to gamma oscillations, as measured by EEG during a working memory task, and found that both baseline and working memory-induced gamma oscillations were strongly dependent on GABA levels either in patients and controls (36). Within a data rich experimental design, the second multimodal study integrated *in vivo* MRS measurements of hippocampal GABA (and glutamate) concentration in patients with *in vitro* tissue biochemistry (sampling postmortem human hippocampal tissue) and MRS on a mouse model recapitulating symptoms of SZ (dentate gyrus-selective knockout of the GRIN1 gene, encoding a critical unit of *N*-methyl-D-aspartate receptors) (28). Looking at *in vivo* MRS results, authors found no global difference in GABA level between SZ and HC both in humans and animals, while they found decreased glutamate in SZ. Looking at *in vitro* results, authors found reduced level of GluN1 protein, a marker of the glutamatergic system, in SZ, but no alterations with respect to HC in the level of GAD67, the main enzyme in the GABAergic system. The combination of such findings provides evidence that the excitatory, but not the inhibitory, system within the hippocampus is implicated in SZ pathogenesis.

Finally, three studies found increased GABA concentration in SZ with respect to HC. One of them compared unmedicated SZ and patients medicated only with atypical antipsychotics to HC (37). Authors showed increased prefrontal GABA in unmedicated SZ patients with respect to both medicated and HC samples. Such results partially confirmed those presented in a previous research in which, averaging GABA concentration in anterior cingulate cortex (ACC) and parieto-occipital cortex (POC), authors found increased GABA in chronic SZ (38). More recently, an increased GABA concentration in dorsal caudate area and medial prefrontal cortex has been observed also considering ultra HR patients free from GABA modulating medications (GMM) (i.e., benzodiazepines, mood stabilizers, or antidepressants) and antipsychotics (39).

Bipolar Disorder

Among the few studies using MRS to measure GABA concentration in BD, three reported no difference between patients and HC (40–42). However, papers contributing to such evidence are very heterogeneous in terms of localization of MRS voxel, clinical characteristics of BD samples, and GMM (see **Table 2**), which were scarcely considered in the analyses. Their effect was specifically taken into account in a study indicating an increased GABA in BD as a whole, with respect to HC. However, within the patients group, there was a reduction of GABA in those taking GMM (43). To clarify the impact of medication dosage and lifetime exposure on GABA concentration, some authors considered only drug free patients (for at least 3 months before MR scan) who however, had lifetime exposure to lithium, antidepressants, or mood stabilizers (44). Results indicated decreased GABA level in recovered unmedicated BD patients with respect to HC.

No study using multimodal techniques has been published so far on BD patients.

Unipolar Major Depressive Disorder

Studies investigating unipolar MDD patients showed either no difference in GABA concentration between patients and HC (45–50), either a reduction of GABA in MDD (44, 51–54). A decreased GABA level has been observed mainly in patients depressed at scan time (51–53), but some authors found a reduction also in remitted patients (44, 54). One study comparing GABA level between HR subjects (i.e., having a family history of parental depression) and a control group without a family history of depression described negative results (45). Among studies failing to find an alteration of GABA in MDD, one combined genotyping with MRS in order to test the effect of common variants of the tryptophan hydroxylase isoform 2 (TPH2) gene, modulating serotonergic neurotransmission and brain circuits for emotion and adaptation, on GABA concentration in the prefrontal cortex (PFC) (47). Authors found a significant association between increased GABA concentration in the PFC and the allele frequencies of three TPH2 SNPs in female subjects, independently from diagnosis. Along with MRS, another research focused on remitted, formerly severe MDD patients and HC using MEG to measure the induced gamma oscillation frequency (IGF), a reliable surrogate marker of postsynaptic GABA function, in the OC (49). Authors found that MDD have normal IGF and GABA concentration in the OC. In a further multimodal investigation, MRS quantifying GABA, glutamate, and NAA concentrations was combined with fMRI measuring blood oxygenation level-dependent (BOLD) response to emotional stimuli in the pregenual ACC, part of the default mode network, related to anhedonia (48). MRS results showed no alteration in metabolites concentration in MDD patients, while fMRI indicated that negative BOLD responses, as well as glutamate and *N*-acetylaspartate concentrations, correlated with emotional intensity ratings, an anhedonia surrogate, in MDD but not in HC. Differently, negative BOLD responses in HC

TABLE 2 | Studies comparing GABA concentration between mood disorders patients (BD and MDD) and HC.

Reference	Sociodemographic characteristics				Clinical characteristics			Probed brain region	Brain region of altered GABA in patients	Additional findings	Other techniques
	Sample size		Age [mean (SD) or years range]		Illness duration (mean (SD) or years range)	GMM [no. patients (%)]	Antipsychotics [no. patients (%)]				
	Patients	HC	Patients	HC							
BD											
BD < HC											
Bhagwagar et al. (44)	16 BD-I, 15 rMDD	18	BD-I = 37.0 (13.8), rMDD = 42.1 (14.6)	37.6 (14)	BD-I = 0.5–10.1, rMDD = 1–18.4	Medication free for $T \geq 3$ months: 32 (100), Lifetime exposure: BD-I: antidepressant: 11 (69); lithium: 6 (37); mood stabilizers: 3 (19). rMDD: antidepressant: 10 (62); lithium: 1 (6)	Na	OC	OC	GABA_rMDD = GABA_BD-I	
BD = HC											
Soeiro-de-Souza et al. (40)	50	38	31.7 (9.1)	25.7 (5.7)	Na	anticonvulsants: 23 (46); antidepressants: 8 (16); benzodiazepines: 1 (2); lithium: 29 (58)	Atyp: 23 (46), Typ, Both: Na; None: 0 (0)	ACC			
Godlewska et al. (41)	13	11	23.8 (3.6)	21.9 (2.7)	Na	Mood stabilizers naive: 13 (100)	None: 13 (100)	MPFC, OC			
Kaufman et al. (42)	13	11	40.5 (12.5)	41.2 (14.0)	18.4 (11.4)	Antidepressant: 6 (46), mood stabilizers: 12 (92)	Typ, Atyp, Both: Na; None: 0 (0)	POC, Thal, whole brain		Whole brain: GABA_BD_antipsy < GABA_BD_noantipsy	
BD > HC											
Brady et al. (43)	14 BD-I	14	32.6 (13.6)	36.9 (10.4)	8.7	Anticonvulsants: 5 (36); antidepressants: 7 (50); benzodiazepines: 6 (43); lithium: 4 (29)	Typ: 2 (14); Atyp: 9 (64); Both: Na; None: 0 (0)	ACC, POC	ACC, POC	GABA_HC < GABA_BD-I_GMM < GABA_BD-I_nGMM	
MDD											
MDD = HC											
High risk patients											
Taylor et al. (45)	24 HR	28	18.9 (16–21)	19.8 (17–21)	0	Drug naive: 24 (100)	None: 24 (100)	POC			
Patients depressed at scan time											
Godlewska et al. (46)	39	31	29.9 (10.6)	30.3 (10.6)	Na	6 weeks FU: antidepressant (escitalopram): 39 (100)	T0: None: 39 (100)	OC		T0: GABA_MDD = GABA_HC GABA_MDD_T0 = GABA_MDD_FU	
Preuss et al. (47)	19 cMDD, 16 rMDD, 9 PD	20	cMDD: 31.5 (9), rMDD: 40.8 (11.7), PD = 33.8 (12.8)	36.9 (13.8)	Na	Psychotropic medication free for $T > 4$ weeks: 44 (100)	None	PFC		GABA level differs between female carrier/non-carrier of 3 nuclear polymorphysms	Genotyping

(Continued)

TABLE 2 | **Continued**

Reference	Sociodemographic characteristics				Clinical characteristics			Probed brain region	Brain region of altered GABA in patients	Additional findings	Other techniques
	Sample size		Age [mean (SD) or years range]		Illness duration (mean (SD) or years range)	GMM [no. patients (%)]	Antipsychotics [no. patients (%)]				
	Patients	HC	Patients	HC							
Walter et al. (48)	19 (11 with MRS GABA level)	24 (13 with MRS GABA level)	40.0 (Na)	34.6 (Na)	Na	Psychotropic medication free for $T > 1$ week: 19 (100)	Na	ACC		GABA_HC correlated with NBR, but not GABA_MDD	fMRI
Patients remitted at scan time											
Shaw et al. (49)	19	18	23 (2.6)	21 (1.5)	Na	Medication free: 19 (100)	Na	PFC, OC, ltBG		OC: IGF_rMDD = IGF_HC	MEG
Hasler et al. (50)	16	15	41.0 (11.6)	41.7 (12.4)	Na	Antidepressant medication free for $T \geq 3$ months: 16 (100)	Na	DM/DA-PF, VM-PF			
MDD < HC											
Patients depressed at scan time											
Gabbay et al. (51)	20	21	16.7 (2.7)	16.2 (1.6)	11.7 (8.6) months	Psychotropic medication free for $T \geq 3$ months: 20 (100)	Na	ACC	ACC		
Price et al. (52)	15 TRD, 18 nTRD	24	TRD = 46.8 (11.9), nTRD = 38.3 (12.3)	37.25 (13.5)	TRD: 26.93 (10.8), nTRD: 21.80 (16.4)	Psychotropic medication-free for $T \geq 2$ weeks: TRD + nTRD: 33 (100)	Na	OC, ACC	OC	OC: GABA_MDD (TRD + nTRD) < GABA_HC GABA_TRD < GABA_HC GABA_nTRD = GABA_HC	
Hasler et al. (53)	20	20	34.0 (11.2)	34.8 (12.4)	18.8 (13.5)	Medication free for $T > 4$ weeks or medication naive: 20 (100)	Na	DM/DA-PF, VM-PF	DM/DA-PF		
Patients remitted at scan time											
Bhagwagar et al. (54)	12	11	40.6 (4.2)	34.3 (4.1)	Na	Medication free for $T > 6$ months: 12 (100)	Na	ACC, POC	ACC, POC		
Bhagwagar et al. (44)	16 BD-I, 15 rMDD	18	BD = 37.0 (13.8), rMDD = 42.1 (14.6)	37.6 (14)	BD-I: 0.5–10.1, rMDD: 1–18.4	Medication free for $T \geq 3$ months: 32 (100), Lifetime exposure: BD-I: antidepressant: 11 (69); lithium: 6 (37); mood stabilizers: 3 (19). rMDD: antidepressant: 10 (62); lithium: 1 (6)	Na	OC	OC	GABA_ rMDD = GABA_BD-I	

ACC, anterior cingulate cortex; Atyp, patients taking atypical antipsychotics; BD, bipolar disorder patients; BD_antipsy, patients taking antipsychotics; BD-I_GMM, BD-I patients taking GABA modulating medications; BD-I, patients with bipolar disorder type I; BD_noantipsy, patients not taking antipsychotics; BD-I_nGMM, BD-I patients not taking GABA modulating medications; cMDD, patients with a current episode of major depressive disorder; DM/DA-PF, dorsomedial/dorsal anterolateral prefrontal region; fMRI, functional magnetic resonance imaging; FU, follow up; GMM, GABA-modulating medication; HC, healthy controls; HR, high risk patients; IGF, induced γ frequency; ltBG, left basal ganglia; MEG, magnetoencephalography; MDD, major depressive disorder patients; MPFC, medial prefrontal cortex; Na, not available; NBR, negative blood response; nTRD, non-treatment-resistant depression; OC, occipital cortex; PD, panic disorder; PFC, prefrontal cortex; POC, parieto-occipital cortex; rMDD, individuals with remitted major depressive disorder; SD, standard deviation; T, time; T0, baseline; Thal, thalamic region; TRD, treatment-resistant depression; Typ, patients taking typical antipsychotics; VM-PF, ventromedial prefrontal region.

correlated with GABA. The fact that GABA concentration could not differentiate between MDD patients and HC together with the absence of GABA modulating effects on anhedonia were interpreted as secondary outcomes consequent to a primary deficit in glutamatergic metabolism, which may lead to a distortion of the excitation–inhibition balance and cause anhedonic depression.

DISCUSSION

The involvement of GABA abnormalities in the mechanisms of psychiatric disorders is strongly debated. In particular, recent developments in MRS sequences allow discriminating the peak of GABA from those of more concentrated metabolites in the brain, thus permitting its measurement. However, despite postmortem evidence and preclinical studies highlighting GABAergic abnormalities in patients with mental disorders, the connection between these abnormalities and categorical/diagnostic or dimensional/symptomatic characteristics is still unclear. In this framework, we reviewed the body of evidence on GABA concentration, as measured by MRS in localized brain regions of SZ, BD, and MDD patients, particularly highlighting results obtained by multimodal methods and multiple experimental techniques.

Although this topic is under continuous development, some conclusions can be drawn from the present results.

Schizophrenia

First, the reduction of GABA level in SZ (the most frequent reported result) seems to occur in specific brain areas (frontal, occipital, and basal ganglia) and in old age, being probably a mixed effect of chronicity, lifetime exposure (more than current type or dosage) to antipsychotics, and GMM, particularly benzodiazepines (17). The latter is known to allosterically increase $GABA_A$ receptor activation, but available experimental techniques are still too coarse to detect circuit-specific perturbations in GABA levels as induced by benzodiazepines (or other medications modulating neuronal transmission), and results are not concordant. From our review, a slight majority of authors failed to find a link between GABA level and medications. Such heterogeneous results might be reconciled performing technically more precise experiments (e.g., MRS at ultra high magnetic field) and enrolling HR subjects in their preclinical stage or drug naive patients to be followed longitudinally.

The second interesting conclusion derived from multimodal studies on SZ is that GABA concentration alone cannot be considered a biomarker for this disorder, while a potential perturbation in the balance between excitation and inhibition, measurable through glutamate/GABA ratio, needs to be more deeply investigated in SZ (28). The latter should be the target for studies aimed at clarifying mechanisms and/or novel therapeutic strategies.

Bipolar Disorder

Unfortunately, GABA cannot be considered a biomarker of BD yet. Indeed, the only study including young and drug naive patients failed to find differences with respect to HC (41). From the other few studies, it appears that both current and lifetime exposure to GMM tend to reduce GABA level in BD patients, especially in the OC (43, 44). However, heterogeneity of patients' clinical characteristics, illness phase at scan time, number of previous manic/depressive episodes, and eventual action of the complex mixtures of GMM (not only benzodiazepines but also antidepressants, lithium, mood stabilizers, etc.) justify the need to start multimodal researches focused on more homogeneous clinical subsamples.

Major Depressive Disorder

Research on neurotransmission in MDD is truly promising and intriguing in the hunt for innovative approaches to prevention. Understanding whether eventual changes in GABA reflect an underlying trait vulnerability to depression, or can be considered "scars" of depressive episodes or treatment effects, may have implications for preventative strategies in HR subjects (55). The only study measuring GABA concentration with MRS in subjects at risk of depression did not find differences in the parieto-occipital cortex with respect to subjects not at risk, indicating that, at the actual level of accuracy, GABA level in such brain region cannot be considered an endophenotype for depression (45). Moreover, the study including genotyping showed that GABA concentration in PFC is associated with allele frequencies of three polymorphisms linked to anxiety only in women, independently from the diagnosis (47). This result reinforces the notion that GABA levels are not a marker of MDD (at least in the POC and PFC). The other two multimodal studies associating MRS with fMRI (48) and MEG (49) failed to find differences in GABA concentration in diffuse brain regions between MDD and HC. However, the classification of studies in terms of patients state (i.e., depressed/remitted) at scan time (see **Table 2**) allows us to support the idea that GABA level identifies the state of being ill, and is not a trait marker for diagnosis, since physiological concentration has been described in the majority of studies including MDD patients during the remission phase (44, 49, 50, 53, 54). Conversely, a primary deficit in glutamatergic metabolism may cause aberrant neuronal activations patterns in regions specifically relevant for the expression of anhedonic behavior in MDD.

CONCLUSION

Complex and multimodal researches looking at GABA in psychiatric populations are still a minority. Our review shows that fMRI, *in vitro* biochemistry, genotyping, EEG, and MEG have been combined to MRS, and each of them adds a piece to the puzzle depicting the role of GABA abnormalities in psychiatric disorders. Indeed, fMRI can differentiate neural response patterns induced by stimulation (56), *in vitro* biochemistry allows higher resolution spatial information and correlations between MRS results and biochemical activity of the brain, while genotyping can elucidate the genetic correlates of GABAergic transmission. Furthermore, as EEG reflects voltage changes resulting from the synchronous firing of groups of neurons (57), and MEG describes the effects of synchronous postsynaptic activity (58), when combined with MRS they allow the *in vivo* investigation of GABA effect on neuronal transmission. Thus, from studies using a multimodal approach, it appears that GABA level alone may not be the best biomarker for the psychiatric disorders here considered. However, it is a promising parameter, particularly for the stratification of patients in more homogeneous subtypes

sharing specific biological features. The possibility to reduce heterogeneity in psychiatric patients is fundamental both in research (giving the opportunity to gain new insight in the underlying pathophysiology of different mental disorders) and in clinical practice (allowing the prescription of effective and tailored medical treatments).

Conversely, although still scarce, the so-called third-generation paradigms will be the turning point of neuroimaging research on neurotransmission in general, and on GABA dysfunctions in particular. The effort spent in the design and realization of multimodal studies, as well as multicentre ones to include larger samples, would then be rewarded by the strong translational impact of such researches. This approach would support clinicians in the design of preventative interventions with defined, expected outcomes for specific types of psychiatric patients making "precision medicine" a more realistic medical model. The precise medicine is the final end.

AUTHOR CONTRIBUTIONS

CCh and GS conceived the paper and performed literature search. CCh, FeP, FaP, and GS wrote the paper. All authors critically reviewed the manuscript and agreed on its final version.

FUNDING

This study was supported by the FILAS-RU-2014-1092 (PAMINA) grant of Regione Lazio.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 19 April 2016
doi: 10.3389/fpsyt.2016.00063

Multimodal Neuroimaging-Informed Clinical Applications in Neuropsychiatric Disorders

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Recent advances in neuroimaging data acquisition and analysis hold the promise to enhance the ability to make diagnostic and prognostic predictions and perform treatment planning in neuropsychiatric disorders. Prior research using a variety of types of neuroimaging techniques has confirmed that neuropsychiatric disorders are associated with dysfunction in anatomical and functional brain circuits. We first discuss current challenges associated with the identification of reliable neuroimaging markers for diagnosis and prognosis in mood disorders and for neurosurgical treatment planning for deep brain stimulation (DBS). We then present data on the use of neuroimaging for the diagnosis and prognosis of mood disorders and for DBS treatment planning. We demonstrate how multivariate analyses of functional activation and connectivity parameters can be used to differentiate patients with bipolar disorder from those with major depressive disorder and non-affective psychosis. We also present data on connectivity parameters that mediate acute treatment response in affective and non-affective psychosis. We then focus on precision mapping of functional connectivity in native space. We describe the benefits of integrating anatomical fiber reconstruction with brain functional parameters and cortical surface measures to derive anatomically informed connectivity metrics within the morphological context of each individual brain. We discuss how this approach may be particularly promising in psychiatry, given the clinical and etiological heterogeneity of the disorders, and particularly in treatment response prediction and planning. Precision mapping of connectivity is essential for DBS. In DBS, treatment electrodes are inserted into positions near key gray matter nodes within the circuits considered relevant to disease expression. However, targeting white matter tracts that underpin connectivity within these circuits may increase treatment efficacy and tolerability therefore relevant for effective treatment. We demonstrate how this approach can be validated in the treatment of Parkinson's disease by identifying connectivity patterns that can be used as biomarkers for treatment planning and thus refine the traditional approach of DBS planning that uses only gray matter landmarks. Finally, we describe how this approach could be used in planning DBS treatment of psychiatric disorders.

Keywords: deep brain stimulation, machine learning applied to neuroscience, multimodal imaging, individual variability, precision psychiatry

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Heather C. Whalley, University of Edinburgh, UK
Niklaus Denier, University of Basel, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *22 January 2016*
Accepted: *29 March 2016*
Published: *19 April 2016*

Citation:
O'Halloran R, Kopell BH, Sprooten E, Goodman WK and Frangou S (2016) Multimodal Neuroimaging-Informed Clinical Applications in Neuropsychiatric Disorders. Front. Psychiatry 7:63. doi: 10.3389/fpsyt.2016.00063

INTRODUCTION

The neuropathology underlying psychiatric disorders is poorly defined, and, consequently, psychiatric nosology is mainly informed by clinical observation. As a result, psychiatric diagnoses are likely heterogeneous, multifaceted, and overlapping in their etiology and pathophysiology (1). This motivates efforts to characterize valid and reliable biological markers of disease expression in order to facilitate early identification and novel treatment discovery. Neuroimaging has already had a transformative role in psychiatry, as it has established that psychiatric disorders are disorder of the brain. Magnetic resonance imaging (MRI) methods, and particularly functional MRI (fMRI), diffusion-weighted, and diffusion tensor imaging (DWI/DTI), have been extensively used to assess alterations in brain functional and structural organization associated with psychiatric disorders (2, 3). Findings from the neuroimaging literature have improved the characterization of the biological underpinnings of psychiatric disorders but have had limited clinical utility, as they are based on group-level inferences that cannot be readily applied to single individuals (4).

The term "third-generation imaging" collectively describes the development of new paradigms in image acquisition and analysis that aim to identify brain markers that can improve diagnostic assessment and prognostic formulations and lead to personalized treatment planning (4). In this article, we highlight the potential of multivariate pattern recognition methods to address areas of diagnostic and prognostic uncertainty in mood disorders, and we then focus on the promise of high-field imaging in leading to identification and targeting of patient-specific neural targets.

MULTIVARIATE PATTERN RECOGNITION METHODS IN PSYCHIATRIC DISORDERS

The majority of neuroimaging studies in psychiatry use voxel-based statistics (e.g., general linear model), which are biased toward detecting group-level differences that are highly localized in space and linear in nature. However, structural and fMRI data are inherently multivariate since each imaging dataset contains information distributed among the thousands of its constituent voxels. Over the last 5 years, there has been increasing interest in multivariate pattern recognition methods, as these methods can capture potentially useful information embedded in the spatial pattern of the data. Multivariate pattern recognition can be achieved through several statistical models. Regardless of the model, pattern recognition tools rely on computational algorithms to discover regularities in the data, which are then used to derive rules for inferring individual-level characterization (5) (**Figure 1**). This feature is of translational value, as it is aligned with the person-centered nature of clinical practice. In psychiatric neuroimaging, multivariate pattern recognition methods have been mostly used to classify individuals into discreet categories according to diagnostic status (e.g., patients, healthy controls), prognosis (e.g., converters, non-converters), or treatment response (e.g., treatment responders, non-responders). Frequently used classifiers are support vector machines and Gaussian process classifiers, which use a supervised approach to classification. This means that the algorithm is first trained to identify regularities in the neuroimaging data that discriminate individuals whose status is predefined. For example, the classifier is given imaging data from patients and healthy controls and is trained to generate a classification rule that discriminates the two groups. In the next phase, the test phase, the classifier is presented with a dataset from a previously unseen individual and uses the classification rule to determine the status of this new example. Sensitivity, specificity, and accuracy are the most commonly reported measures of classifier performance in terms of the accuracy of the classification rule in determining the status of previously unseen individual datasets. In the case of binary classifiers, for example, involving patients and controls, sensitivity refers to the proportion of patients (true positives) who are correctly identified as patients, whereas specificity measures the proportion of controls (true negatives) who are correctly identified as controls. The accuracy of the classifier refers to the total proportion of patients and controls that are correctly classified. Furthermore, permutation testing is also employed to determine whether the results of the pattern recognition model deviate significantly from chance. In linear classifiers, voxels can be visualized on the basis of their contribution to classification thus producing discriminative maps (6). The relevant literature in psychiatry has recently been summarized in multiple reviews that provide a comprehensive account of the progress to date and the challenges that still lie ahead (7–10). The field is dominated by studies that sought to discriminate healthy individuals from patients with either schizophrenia ($n = 51$) or major depressive disorder (MDD) ($n = 31$) using structural, diffusion-weighted, and fMRI data; the reported accuracies of these case–control classifiers range between 71 and 96% for schizophrenia and between 61 and 96% for MDD (10).

We focus here on bipolar disorder (BD) where the current evidence base is rather limited despite the fact that BD ranks among the leading causes of disability worldwide across all age groups (11). BD is a mood disorder characterized by episodes of depression and mania and executive function impairments. Our group (12) and other labs (13–17) have tested the value of structural MRI data in discriminating patients with BD from healthy individuals leading to poor (15) or moderate results (12, 16, 17). Investigations using fMRI data from tasks of verbal fluency (18), facial affect processing (19–21), auditory oddball detection (22), and working memory (23) have been more promising, resulting in overall accuracy of approximately 80%. The reported classification accuracies do not appear substantially influenced by the type of task or the neuroimaging features (connectivity measures or whole-brain task-based signal change) used for classification (18–23). This evidence demonstrates the potential utility of pattern recognition models as a diagnostic aid in BD, although it does not address the complexity of diagnostic challenges in clinical settings.

It could be argued that neuroimaging-based tools may prove more useful in situations where clinical assessment and observation alone are known to be insufficient. The diagnostic and prognostic outcome of first-degree relatives of patients with BD presents with several such situations of genuine clinical uncertainty. We therefore tested the hypothesis that neuroimaging,

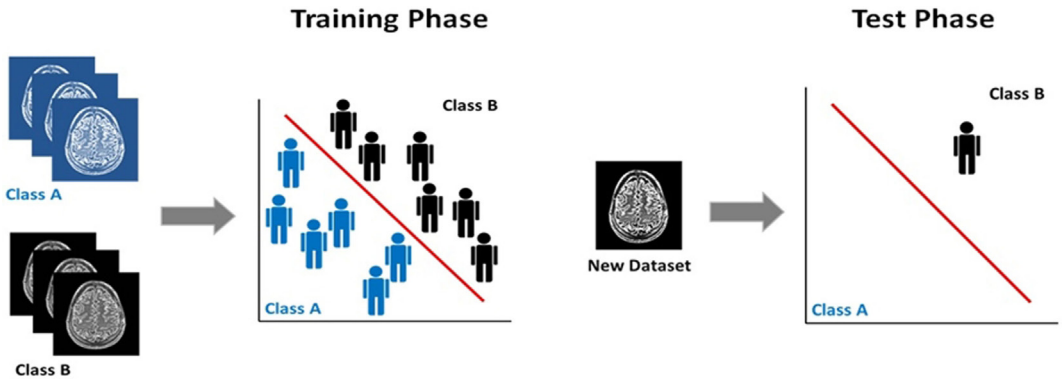

FIGURE 1 | Supervised classification using multivariate pattern recognition models. Classification training and test phase: the classifier in initially trained on a set with predefined class labels and the classification rule derived is used to assign class membership to a previously unseen dataset.

coupled with pattern recognition analyses, might assist in the evaluation of individuals at risk of BD by virtue of a positive family history for this disorder. Genetic proximity to patients remains the most significant predictor of morbidity that is not limited to increased risk for BD but includes other adverse outcomes, most commonly MDD. The respective morbidity risks in first-degree relatives of bipolar patients generally range from 4 to 6% for BD and 11 to 18% for MDD (24). There are two key areas of clinical uncertainty in assessing first-degree relatives of bipolar patients. The first refers to the differential diagnosis of BD from MDD in these individuals. Differentiating these two disorders is generally challenging (25), because the clinical presentation of both disorders is dominated by depressive symptoms (26). There are several demographic and clinical features that are more indicative of bipolar depression but, at the level of the individual patient, depressive episodes arising in the context of BD do not differ substantially from those seen in MDD (27–29). Furthermore, depressive episodes generally precede the onset of the first manic episode by several years (30). It is therefore rather common for individuals with BD to present with depression and to be incorrectly diagnosed as having MDD. The consequences of misdiagnosis include potential worsening of the illness course and greater psychosocial disability (25). In this scenario, it would be helpful to have a diagnostic tool that could differentiate BD from MDD in individuals with positive family history of bipolarity. The second challenge refers to the accurate risk stratification of individuals with a positive family history of BD. As discussed first-degree relatives of patients, as a group, have a higher risk than the general population for affective morbidity (24, 31). However, a substantial number of relatives, up to 60%, may remain free of psychopathology. Correctly identifying individuals who are very unlikely to present with a psychiatric disorder is critical for developing a neuroscience-informed framework for targeted early intervention.

In order to address these issues, we obtained working memory task-related fMRI data from 120 demographically and IQ matched participants consisting of 30 patients with BD-type I (15 men and 15 women, mean age = 34.7 years, SD = 7.7 years), 30 of their first-degree relatives diagnosed with MDD (16 men, 15 women, mean age = 32.9 years, SD = 9.9 years), 30 psychiatrically healthy first-degree relatives (14 men, 16 women, mean age = 35.3 years, SD = 5.6 years), and 30 unrelated healthy controls (15 men, 15 women, mean age = 33.4 years, SD = 11.6 years). Only six participants were related to each other. Participants with BD or MDD were in symptomatic remission at the time of scanning, defined as a total score of <7 in the Hamilton Depression Rating Scale and in the Young Mania Rating Scale. Patients with BD were prescribed atypical antipsychotics ($n = 21$), antiepileptics ($n = 8$), and lithium ($n = 14$), as monotherapy ($n = 18$) or combination therapy ($n = 12$). Three relatives with MDD were on selective serotonin reuptake inhibitors.

Images were acquired using a 1.5-T GE Neuro-optimized Signa MR system (General Electric, Milwaukee, WI, USA) fitted with 40 mT/m high speed gradients. The MRI protocol included a total of 180 T2*-weighted MR brain volumes depicting blood–oxygen level dependent (BOLD) contrast acquired at each of 36 near-axial planes parallel to the inter-commissural plane; repetition time (TR) = 3000 ms, echo time (TE) = 40 ms, slice thickness = 3 mm, voxel dimensions = 3.75 mm × 3.75 mm × 3.30 mm, interslice gap = 0.3 mm, matrix size = 64 × 64, and flip angle = 9°. During the same session, a high-resolution, T1-weighted structural image was acquired in the axial plane [inversion recovery prepared, spoiled gradient-echo sequence; inversion time (TI) = 450 ms, TR = 18 ms, TE = 5.1 ms, slice thickness = 1.5 mm, voxel dimensions = 0.9375 mm × 0.9375 mm × 1.5 mm, matrix size 256 × 192, field of view (FOV) = 240 mm × 180 mm, flip angle = 20°, and number of excitations = 1]. Task-related fMRI data were obtained using the typical letter-based 3-back task in a block design with the 0-back condition as sensorimotor control. We chose the 3-back contrast as in our view, and it represents a selection of an enriched feature for pattern recognition analysis as individual differences in activation patterns are more reliably observed in more demanding task conditions (32). The images were realigned, normalized to the Montreal Neurological Institute (MNI) template, smoothed (using an 8-mm Gaussian kernel), and analyzed using a conventional general linear model. All fMRI data processing and analyses were implemented Statistical Parametric Mapping

(SPM8)[1]. Performance was evaluated in terms of reaction time to target letters and accuracy (% correct responses). Accuracy was 69.8 (16.7) in patients with BD, 73.4 (17.2) in relatives with MDD, 88.5 (14.3) in healthy relatives, and 73.2 (12.4) in healthy controls. The only significant differences concerned the healthy relatives who outperformed all other groups (all $p < 0.01$). Further details of the sample and the paradigm can be found in the original studies (21, 23, 33–48).

Binary Gaussian process classifiers (49) using whole-brain individual beta maps for the contrast of 3-back vs. 0-back were implemented in the Pattern Recognition for Neuroimaging Toolbox (PRoNTo)[2] in order to determine their usefulness in differentiating patients with BD (a) from healthy individuals, (b) from relatives with MDD, and (c) from psychiatrically healthy relatives. Each of these classifiers was trained using a leave-two-out cross-validation iteration, whereby model is repeatedly refit leaving out a pair of observation from each group and then used to derive a prediction for the left-out observations. For each trial, we thresholded the probabilistic predictions at 0.5 to convert the probabilistic predictions to class labels allowing the sensitivity and specificity of classification to be computed over all trials. The statistical significance of each classifier was determined by permutation testing by repeatedly retraining the classifier after permuting the class labels (1000 permutations). A p-value for classification accuracy was computed by counting the number of permutations for which the permuted accuracy was equal or greater than the true accuracy (obtained with non-permuted labels), then dividing by 1000. Each classifier yields a discrimination map with the spatial distribution of voxels that contributed to the discrimination function.

Patients with BD were discriminated from unrelated healthy controls with a sensitivity (true positives for BD) of 84.6%, specificity (true negatives for unrelated controls) of 92.3%, and overall accuracy of 83.5% ($p = 0.001$). The largest clusters discriminating patients with BD from unrelated controls were located in the prefrontal cortex (encompassing the left inferior, middle, and superior frontal gyrus and in the superior parietal lobule). This finding is in line with results reported in other samples of patients with BD using classifiers based on different activation tasks (18–23).

The Gaussian process classifier discriminated patients with BD from their MDD relatives with a sensitivity (true positives for patients with BD) of 53.9%, specificity (true negative for relatives with MDD) of 94.5%, and overall classification accuracy of 73.1% ($p = 0.001$). The largest discriminating clusters were located in the left superior frontal gyrus, right middle frontal gyrus, bilaterally in the middle/superior frontal gyrus, and the right temporal lobe (**Figure 2**). Previous studies have shown that different task-based fMRI classifiers can discriminate patients with BD from unselected patients with MDD with classification accuracy of approximately 80% (10). The present study shows that similar classification accuracy can be achieved even when patients have family history of BD. Importantly, patients with BD and their relatives with MDD could be classified with high specificity. This opens the possibility of excluding the BD, with a very high level of confidence after a 10-min brain scan, when assessing individuals with MDD at high risk for BD by virtue of a positive family history. Clinical application will require replication in different samples and settings and in more diverse clinical populations. Nevertheless, these findings demonstrate the potential value of neuroimaging in assisting in situations of clinical uncertainty.

Patients with BD could be differentiated from their healthy relatives with a sensitivity (true positives for patients with BD) of 72.7%, specificity (true negative for healthy relatives) of 90.9%, and overall classification accuracy of 81.8% ($p = 0.004$). The largest discriminating clusters were located in the lingual/inferior occipital gyrus and the cerebellum on the left (**Figure 2**). The high specificity of the classifier denotes that 90% of high-risk individuals unlikely to convert to BD will be correctly identified. Because of the relatively low sensitivity, some true positives may be missed. The ability to provide personalized risk estimates in individuals at familial risk for BD is essential in designing targeted and cost-effective intervention services and in preventing unnecessary treatment, concern, and self-stigmatization in those unlikely to convert to BD. These results are very encouraging and could potentially inform early intervention services, where positive family history is a key criterion of risk and possible service inclusion (31). At-risk mental states are "pluripotential" as family history of a psychiatric disorder is associated with increased risk for multiple adverse health outcomes. Hence, identifying those unlikely to become unwell may be a more sensible strategy than trying to identify "converters" to a specific diagnosis. The clusters contributing to the correct categorization of healthy relatives in this study show biological plausibility, as previous reports

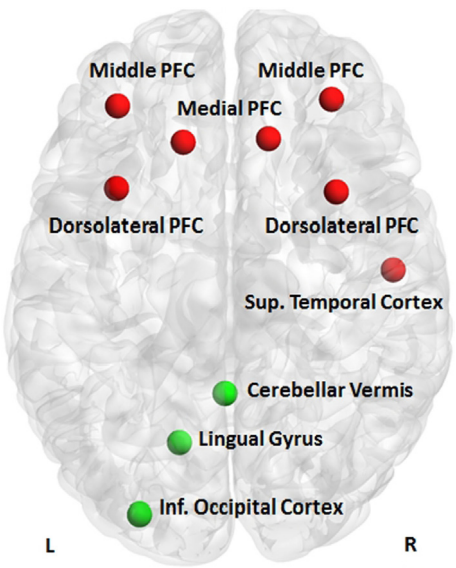

FIGURE 2 | Discriminative clusters. Clusters discriminating patients with bipolar disorder from their relatives with major depressive disorder (red) or their healthy relatives (green); PFC, prefrontal cortex.

[1]www.fil.ion.ucl.ac.uk/spm/software/spm8/
[2]www.mlnl.cs.ucl.ac.uk/pronto/

have shown that the resilient relatives of patients with BD show increased cerebral volume (34) and greater occipital connectivity (49) when compared to patients or unrelated healthy controls.

The data that we present here demonstrate the promise of pattern recognition models, but there are many challenges to overcome before these models are ready for widespread clinical use. A full review is outside the scope of this article, but key challenges involve testing the generalizability of the results in different samples and across different research centers. The issue of medication contributing to the classifier performance cannot be fully accounted or modeled and will require re-evaluation in drug-free samples. A further challenge is providing appropriate training to clinicians and information to the public to deal with the probabilistic nature of machine learning predictions.

An additional challenge relates to individual variability at the level of brain organization. The development of methodological innovations to improve precision in measuring brain phenotypes will greatly assist in moving the field forward. In the next sections, we describe novel approaches designed to capture individual variability thus improving the translational potential of neuroimaging.

PRECISION MAPPING OF STRUCTURAL AND FUNCTIONAL CONNECTIVITY

The increasing availability of high-field MRI scanners, improvements in susceptibility correction methods, and advances in sequence developments enable the *in vivo* investigation of the human brain at higher resolution and higher signal-to-noise ratio than ever before. We illustrate the benefits of high-field imaging using data obtained with DWI/DTI (50), a technique that yields measures of water diffusion within the brain. One DTI-derived measure is fractional anisotropy (FA) that reflects the relative degree to which water diffusion is not evenly restricted in all directions; FA is elevated in areas with high density of white matter tracts due to diffusion being more restricted perpendicular to tracts than along the tracts. **Figure 3** provides a visual comparison of FA maps (**Figure 3**, gray scale images) with the preferred direction of diffusion (**Figure 3**, colored lines) derived from a 7-T compared to a 3-T diffusion-weighted scan. This demonstrates the improvement in the characterization of the anterior limb of the internal capsule (ALIC) and of the boundary between white matter and cortical gray matter with 7-T compared to 3-T.

A consequence of increased resolution is that inter-individual variability in local morphometry and structure–function correspondence becomes more apparent. Individual differences exist in cortical folding as well as in the relationship of cortical curvature and functional localization (51, 52). However, current standard procedures for functional and anatomical analyses rely on normalization of individual brains to common templates based on stereotaxic coordinates and macro-anatomical landmarks. These procedures do not optimally take into account these individual differences, which can lead to misalignment of neuronal activation between subjects (53). As scan resolution increases, allowing for incrementally fine-grained localization of brain function to cortical gyri and sulci within individual brains, the loss of precision due to normalization paradigms becomes more pronounced. Here, we introduce the concept of "precision mapping," an approach that addresses this issue by integrating multiple imaging modalities in a single-subject-centered analysis to identify functionally specialized regions in a way does not require normalization to standard templates.

To illustrate the usefulness of precision mapping, we focus on the connectivity profiles of the nucleus accumbens (NAc) and the ventral prefrontal cortex (vPFC). Precision mapping involves the following four steps. First, white matter seeds and gray matter targets were determined in native space on an anatomical T1-weighted scan (**Figure 4**, step 1). The NAc and the vPFC were defined using Freesurfer[3] segmentation. For the vPFC, multiple Freesurfer regions were combined, and a superior and posterior boundary was identified in MNI coordinate space and transformed to the individual's native space. White matter seeds were selected in MNI space, based on the white matter anterior to the NAc and knowledge from tracer studies (54, 55), and transformed to the individual diffusion space. Second, probabilistic tractography was performed using probtrackX2 in FSL (56) (**Figure 4**, step 2). Third, the endpoints of the tractography were used to identify subregions within the vPFC that is anatomically connected to the NAc, and projected onto the Freesurfer cortical surface to include the full depth of the cortical ribbon (**Figure 4**, step 3). Fourth, the tractography-determined vPFC subregions and the corresponding subcortical targets were affine transformed to the fMRI space and used for functional connectivity analyses (**Figure 4**, step 4). The MNI space is only used for the identification of seed regions as a starting point for tractography, but all further processing is completely template independent and therefore individual specific. Thus, the defined network regions can vary in exact location and shape depending on the morphology of the tracts and the cortical surface within each individual.

There are three critical advantages of precision mapping for psychiatric research and treatment development:

(a) Retention of the individual variation: precision mapping does not depend on common neuroanatomical templates or standard atlases. All analyses are performed in each individual's native space, and affine transformations are only applied to coregister the volumes across the anatomical, diffusion, and functional acquisitions.
(b) Optimized identification of functionally homologous regions: precision mapping defines functionally homologous regions by relying on regional anatomical "connectivity fingerprints" (57), which closely correspond to regional functional specialization at very fine-grained scales in the human brain, the animal brain, and at the neuronal level *in vitro* (58–60). This approach thus enables the identification of functionally homologous regions across individuals, without requiring stereotaxic uniformity of functional organization.
(c) Improved alignment of structural and functional connectivity. Precision mapping allows the identification of individual-specific direct anatomical connections between

[3]http://surfer.nmr.mgh.harvard.edu/

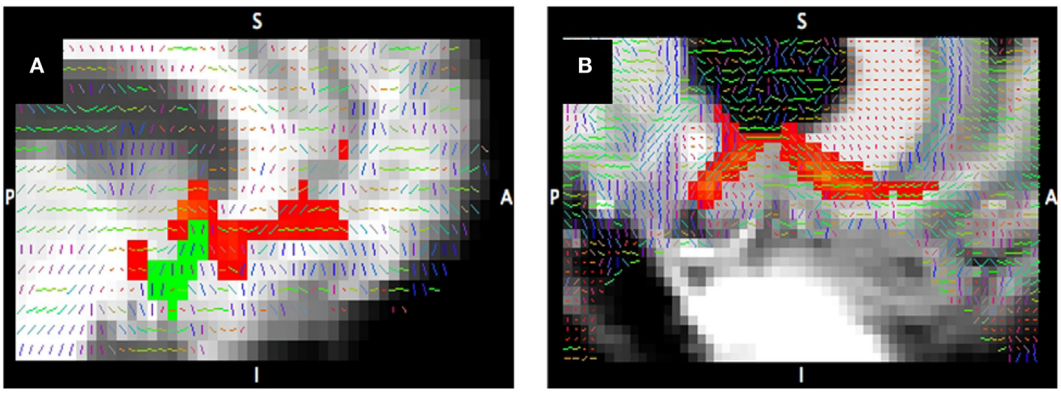

FIGURE 3 | Tractography at 3-T compared to 7-T. Tracts connecting the nucleus accumbens (shown in green) to the ventral prefrontal cortex from diffusion-weighted imaging at 3-T **(A)** and 7-T **(B)**. Tract probability map >1% of streamlines (red) corrected for distance; primary diffusion direction overlaid on T1-weighted image.

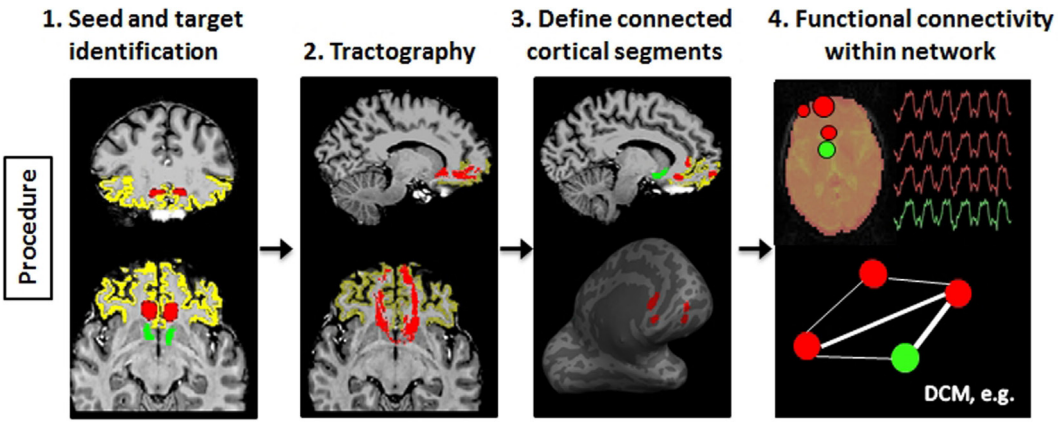

FIGURE 4 | Schematic illustration of the processes involved in precision mapping. Step 1: seeds (red) and targets (vPFC: yellow; nucleus accumbens: green) are identified in native space. Step 2: probabilistic tractography is performed. The tract is binarized at 1% of the maximum value (red). Step 3: the segments (red) of the vPFC that is connected to the nucleus accumbens are identified and transformed to the cortical surface in order to include the entire depth of the cortex. Step 4: the cortical segments and the nucleus accumbens segmentation are transformed to the native functional MRI space, and BOLD time series are extracted to perform functional connectivity or dynamic causal modeling (DCM) analysis of the tractography-defined network.

brain regions of interest. This yields a more complete picture of the functional interactions between regions compared to standard group-based functional connectivity analyses.

The multimodal nature of precision mapping is ideally suited to investigate multiple potential causes of network dysfunction within and across individual patients. Qualitative inspection of the data may be on occasion sufficient to identify unusual connectivity segments and can be supplemented by quantitative analyses. Given a large enough sample, the extracted metrics of functional connectivity, anatomical connectivity, and gray matter density may be used to uncover dimensions or different types of network dysconnectivity or (dys)function within patient populations, as well as their variability healthy individuals (**Figure 5**). Precision mapping is a first step on a new route to clinically translational neuroimaging that can yield an understanding of the nature of brain network pathology in individual patients and its variability between patients.

PRECISION TARGETING OF PATIENT-SPECIFIC TARGET NETWORKS FOR TREATMENT

In neurological disorders, neuroimaging has enabled the successful application of neurosurgical treatments particularly deep brain stimulation (DBS). DBS has been approved by the Food and Drug Administration (FDA) under a humanitarian device exemption for the treatment of movement disorders, such as Parkinson's disease (PD), dystonia, and essential tremor. Although medications can be remarkably effective at controlling symptoms, DBS is the currently the most effective option to control symptoms

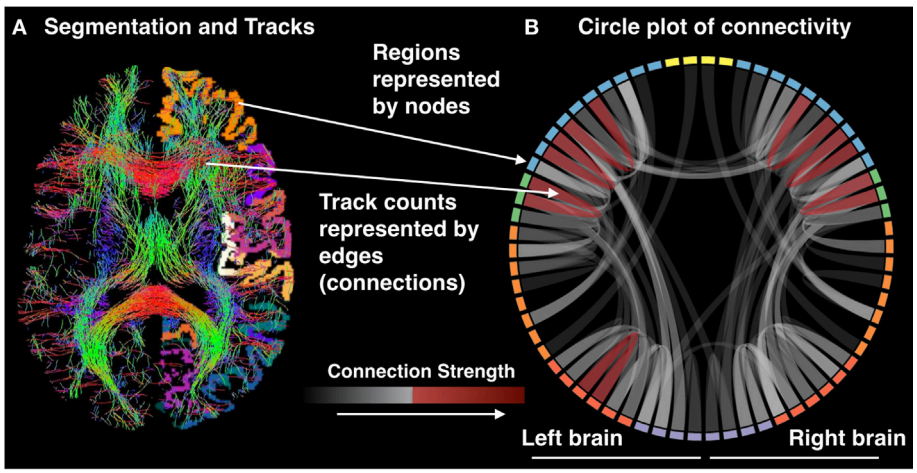

FIGURE 5 | **(A)** Segmentation and tracks and **(B)** circle plot of connectivity.

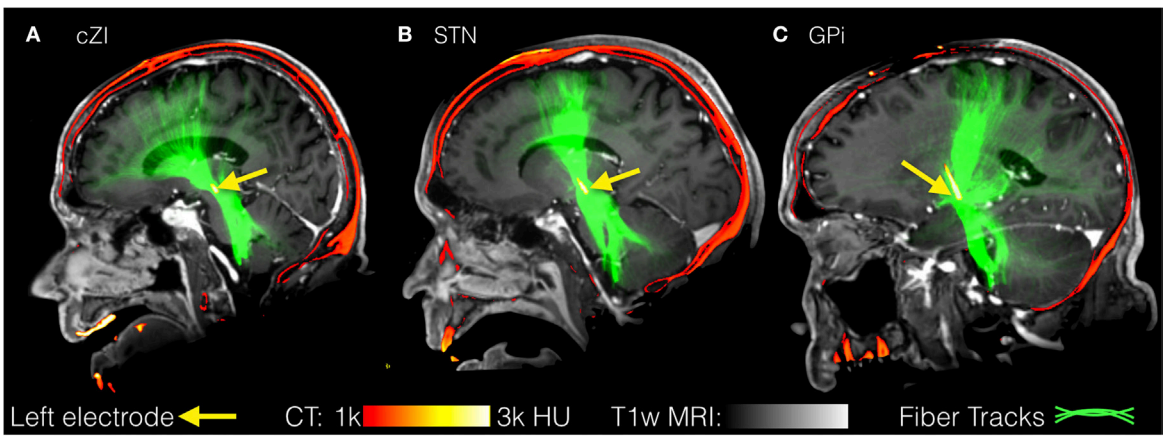

FIGURE 6 | **Fiber tracks from three separate patients with electrodes targeting either the caudal zona incerta (cZi) (A), the subthalamic nucleus (STN) (B), or the globus pallidus interna (Gpi) (C)**. These sagittal views show the fiber tracks that pass through a 3-mm sphere centered on the active electrode and may represent fibers of passage most affected by deep brain stimulation (DBS).

and increase quality of life for patients who are refractory (61, 62). The improved efficacy of DBS relies on the targeting of the circuits involved in PD that connect key subcortical nuclei and particularly the globus pallidus interna (GPi), the subthalamic nucleus (STN), the caudal zona incerta (cZi), the red nucleus, and the substantia nigra (61–64). As such, the success of the surgery depends critically on the exact location of the implant in relation to these key brain structures. Visualization of the target circuitry is commonly achieved by sensitizing the MRI signal to the presence of either myelin or iron. Myelin provides contrast between gray and white matter, whereas iron (accumulated in dopaminergic neurons) provides contrast in the basal ganglia and key nuclei of interest in DBS. In conventional DBS, planning lead placement is determined in reference to structures delineated by their myelin and iron content. Although relatively high success rates are achieved by this method, there are cases in which outcomes are suboptimal. A potential explanation for this is that current techniques fail to fully characterize the white matter, and the tissue is composed of highly myelinated axons. Axons are of high relevance to DBS, because they are the most sensitive element of the neuron to the stimulation (65–68). The white matter forms the structural scaffolding of all brain networks. Thus, local stimulation of a key white matter tract with DBS can be thought of as affecting a network whose edges are composed of the fibers of passage around the active electrode. The efficacy of DBS may therefore depend on targeting those white matter tracts that connect and can therefore modulate activity in multiple key multiple regions of disease-related circuits. Direct empirical support for the role of local stimulation has recently been provided in a mouse model of PD using optogenetics and solid-state optics (69). In this model, direct selective stimulation of axonal afferents to the SNT was associated with therapeutic response. Therefore, precision targeting for white matter tracts is important for DBS in humans. White matter tractography was introduced to the field

of DBS about a decade ago but has yet to be widely adopted as shown in a recent review that identified only 15 studies with just 66 patients (69). Accumulating evidence, however, suggests that tractography may prove an essential part of treatment planning as the efficacy of DBS is closely associated with the accuracy of lead placement in relation to the target brain regions. For example, Coenen et al. (70) reported that treatment efficacy in patients with PD, essential tremor, and myoclonus dystonia was associated with lead placements close to or within the dentato-rubrothalamic tract (DRT). MDD offers another example where variability in DBS outcome has been closely associated with target selection; recent evidence suggests that DBS treatment success may critically depend on electrode placement in the confluence of the uncinate faciculus, forceps, and cingulum bundle (71). Hartmann and colleagues (72) used innovative computational tractography-based activation models to determine the network

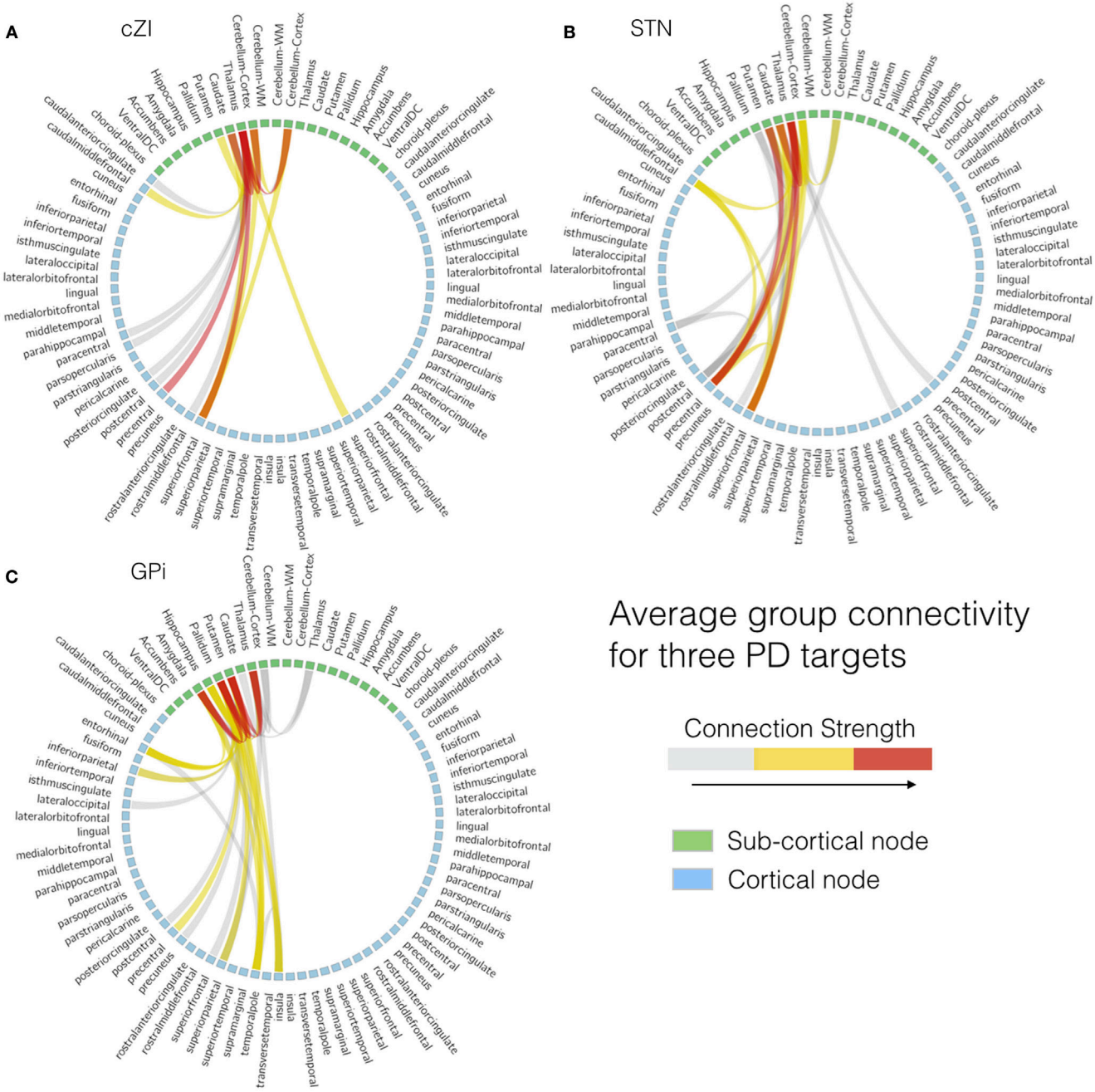

FIGURE 7 | **Individual patient connectivity plots based on electrode location**. Structural connectivity plots from three separate patients with electrodes targeting either **(A)** the caudal zona incerta (cZi), **(B)** the subthalamic nucleus (STN), or **(C)** the globus pallidus interna (Gpi).

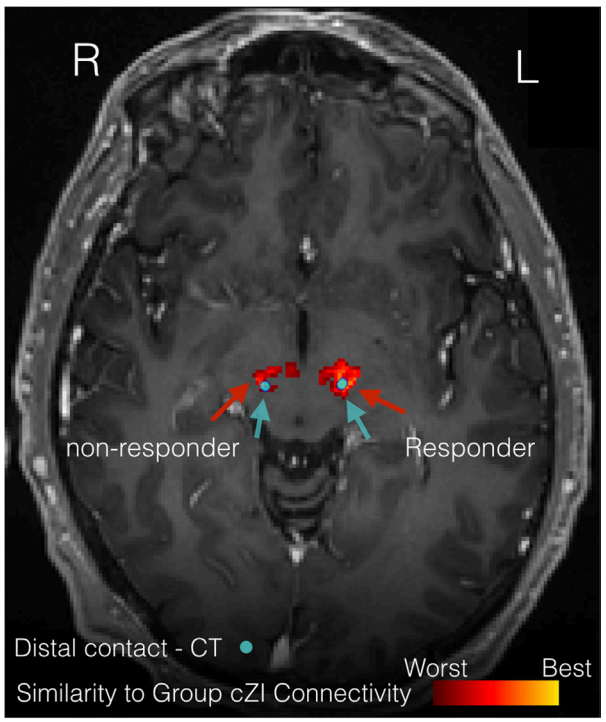

FIGURE 8 | Precision targeting at the individual patient level. The figure illustrates the difference between patient-specific connectivity and group connectivity to guide targeting for a patient where the caudal zona incerta (cZi) has been targeted. The heat map shows where this patient's connectivity is the closest match to the group connectivity average in patients having a good treatment response. The actual location of implants is shown on the postoperative computerized tomography (CT) scan (blue).

effects of DBS targets to the NAc and ALIC in patients with obsessive compulsive disorder (OCD). They showed that therapeutic response in OCD patients show tract selectivity. Similar findings in OCD have also been reported by Makris and colleagues (73). Identification of the target tract for DBS implantation is further complicated by the intricate connectivity profiles of many subcortical DBS targets as is the case with GPi, for example, whose connectivity pattern varies along the dorsal to ventral dimension with dorsal GPi regions being more connected to motor regions (74, 75). Precision targeting is therefore essential for the correct identification of the white matter DBS targets.

We focus first on PD because the brain networks involved in disease expression are well-characterized and are known to involve the striatum, pallidum, and midbrain. Nevertheless, at the level of the individual patient, both target network selection and optimal electrode placement remain a challenge. The reason for this may lie in the unique white matter anatomy of each patient and the fact that these deep, centrally located nodes of the network are highly connected "hubs" that serve many functions (76).

In order to explain the efficacy and side effects of DBS, we propose to establish connectivity profiles associated with three common targets for the treatment of PD, namely, the cZI, STN, and GPi (60–63). To do this, the connectivity profiles 17 PD patients who underwent bilateral DBS implantation (5 patients with cZI, 7 patients with STN, and 5 patients with GPi targets) were computed and compared. All patients provided informed consent in accordance with a protocol approved by our institutional review board. All patients were imaged preoperatively with MRI under general anesthesia on a 3-T GE MRI magnet (Discovery 750, GE Healthcare, Waukesha, WI, USA) with a 8-channel receive-only head coil (*Invivo* Corp., Gainesville, FL, USA). The MRI protocol included, a T1-weighted sequence for identifying structure and segmentation, DWI for white matter characterization, quantitative susceptibility mapping (77) to identify iron-rich deep brain nuclei, and contrast-enhanced angiography to identify vessels to be avoided during surgical planning. DWI was performed using a dual spin echo sequence with 60 independent diffusion-encoding directions ($b = 1000$ s/mm^2) and 5 unweighted images, with in-plane resolution of 2 mm × 2 mm × 3 mm over 61 slices, TR/TE = 7200/82 ms. T1-weighted imaging was performed using an inversion-prepared fast spoiled gradient echo sequence (BRAVO FSPGR) with FOV = 24 cm, resolution 1 mm × 1 mm × 1.2 mm over 164 slices, TR/TE/TI = 8.1/3.1/450 ms, and flip angle 10°. On the day of each surgery (surgeries for left and right implants performed on different days), patients were placed in a stereotactic frame (Leksell G Stereotactic Headframe, Elekta, Stockholm, Sweden) and underwent computed tomography (CT) imaging with 280 mAs, 120 kVP, 0.6 mm × 0.6 mm × 1 mm spatial resolution, 1000 ms exposure time, on a clinical CT system (Sensation Cardiac 64, Siemens, Forcheim, Germany). Postoperative CT images were acquired after the removal of the stereotactic frame.

All images were first registered to the first preoperative CT scan using FLIRT (FMRIB Linear Image Registration Tool)[4] and a mutual information cost function. The electrodes were automatically segmented from the second postoperative CT scan (after both electrodes were implanted) using software written in-house in MATLAB (Mathworks, Natick, MA, USA). The segmentation consisted of using a brain mask derived from the structural T1-weighted image to mask out regions outside the brain, then thresholding at 2000 Houndsfield units to obtain only the electrodes. After segmentation, the right and left leads were separately fit to a model of the specific implant (Medtronic 3389 or 3387) to obtain segmentations of the implants including each of the four electrodes and body of the implant. From the segmentation of the electrodes, the centroid of each electrode could be determined. In the structural MR dataset, cortical reconstruction and volumetric segmentation were performed with Freesurfer. The SPGRE image was used as input to Freesurfer. DWI data were corrected for Eddy-current distortions using Eddy_correct in FSL and fit to the preoperative CT using and affine transform. Fiber tracking was performed using the MRtrix package[5]. Constrained spherical deconvolution (78, 79) was performed on preprocessed images to obtain fiber orientation distributions. We used a anatomically constrained probabilistic tractography algorithm (iFOD2) (80) seeded from 3 mm spheres drawn around the centroid of each of the four electrodes, for both the left and right implants, to determine the connectivity pattern of each seed to cortical and

[4]https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT
[5]https://github.com/MRtrix3/mrtrix3

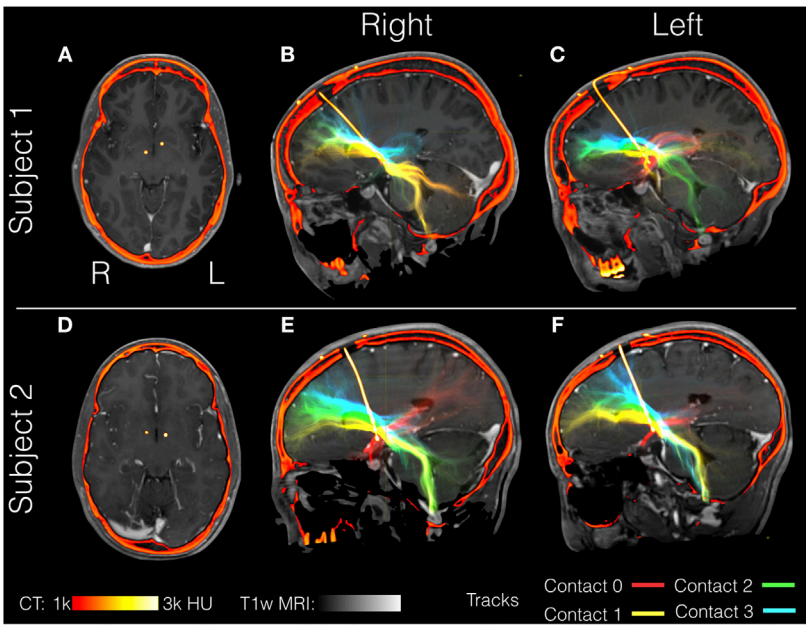

FIGURE 9 | Individual patient tractography based on electrode location in OCD. Tractography from contacts in two patients with obsessive compulsive disorder (OCD), Subject 1 **(A–C)** and Subject 2 **(D–F).** Fiber tracts are color-coded starting from the most distal: contact 0 (red), contact 1 (yellow), contact 2 (green), and contact 4 (blue). Structural T1-weighted MRI is shown in gray, with postoperative computerized tomography (CT) shown in hot colors depicting the skull and the electrode. Axial views show the location of the most distal electrodes **(A,C)** while the sagittal views show the entire electrode including the point it enters the burr hole at the top of the image **(B,C,E,F)**.

subcortical regions using the cortical parcelation and subcortical segmentation algorithms (aparc + aseg) in Freesurfer. **Figure 6** shows fiber tracks from three separate patients with electrodes targeting either cZI, STN, or GPi. These sagittal views show the fiber tracks that pass through the 3-mm sphere centered on the active electrode (cathode) and thus can be interpreted as the fibers of passage most affected by DBS. The tracks from all three targets share some common features as they connect with subcortical regions in the brainstem and cerebellum and with cortical regions within superior prefrontal cortex. We then averaged connectivity matrices from the tracks originating from the active electrode separately for each patient group determined by the DBS target (cZI, STN, and GPi). We focused on the electrode associated with better efficacy and tolerability. Group connectivity plots (**Figure 7**) demonstrate clearly the differences between the three targets. Notably, the cZI and STN targets had strong connections to the contralateral cerebellar cortex that likely encompasses the DRT, as it has a decussation and connects to the contralateral dentate nucleus. Strong connections to the ipsilateral superior frontal cortex may be partly comprised of fibers that form the hyperdirect pathway potentially useful as a target for PD by disrupting the synchrony of sensory motor networks (81).

Figure 8 illustrates the benefits of precision targeting at the individual patient level for one of the cZI patients. In this patient, RMS difference with the average group connectivity from the cZI subjects is shown over the preoperative MRI (**Figure 8**, heat map), with the postoperative CT windowed to show only the implant (**Figure 8**, blue). The best match to the group average coincided almost exactly with the location of the implant on the right side and was approximately 1 mm lateral in the case of the left implant. Note that this surgery was planned in the conventional way without considering DWI. These results show that surgery could be aided by the use of DWI-derived connectivity, displayed in this heat map form which is easy to import into current surgical-planning software.

Deep brain stimulation for the treatment of psychiatric disorders has been gaining more attention since the FDA approved DBS (under a Humanitarian Device Exemption) for the treatment of OCD in 2009 based on evidence that DBS of the ventral internal capsule and ventral striatum may alleviate symptoms in intractable cases of this disorder (82, 83). Since then, DBS has been extensively studied for the treatment of a number of psychiatric disorders, such as MDD and addiction (84). Despite some progress, including insights gained from of a rich body of animal work on basic mechanisms of DBS (85), success in humans has been limited compared to movement disorders. This is primarily because the DBS targets for psychiatric disorders are often located in high order associate cortices where inter-individual variability is greater than for the phylogenetically older subcortical structures targeted in movement disorders. The structures targeted in movement disorders, such as the dorsolateral portion of the STN and the posterolateral GPi, have cortical connections that are very well conserved from patient to patient. By contrast, regions targeted in psychiatric disease, such as the NAc, have high inter-individual variability in their connectivity. Lehman and colleagues (86) demonstrate this clearly using the example of the vPFC, a regions with complex intrinsic functional organization and widespread connections with other cortical and subcortical regions. Their findings are based on conventional

tracing techniques and 3D pathway reconstructions of the white matter connectomic fingerprint of the vPFC in the primate brain. In the preceding section on precision mapping, we discuss the same issue and demonstrate individual variability in vmPFC connectivity in healthy humans. The topographic organization of the efferent and afferent fibers to the vPFC suggests that variations in DBS electrode placement are likely to affect very different cortical and subcortical circuits and that only modulation of a selective subset of fibers may have therapeutic effects (72, 73). This suggests that in psychiatric disorders the ability to characterize individual differences in white matter networks may be even more important than in movement disorders. Thus, the patient-specific, atlas-free approach is applicable and perhaps essential to treatment of psychiatric disease with DBS.

Here, we illustrate the use of precision targeting in two patients undergoing bilateral DBS of the ALIC for the treatment of OCD. Patients gave informed consent to participate in this study in accordance with a protocol approved by our institutional review board. Aside from the target selection, we followed the same imaging procedures, and data processing procedure outlined above for PD patients. OCD patients were implanted bilaterally with Medtronic model number 3391. This lead differed from the models used in the PD patients notably in that the electrode spacing is greater (4 vs. 1.5 mm in the 3387 or 0.5 mm in the 3389) and the contact size is larger (3 vs. 1.5 mm). Fiber tracking from all four contacts in both OCD patients is shown in **Figure 9**. The relative position of the most distal contact to the anterior commissure of each implant is depicted in the axial slices (**Figures 9A,D**). In Patient 1, the right implant from was placed more posterior than the left implant and both implants in Patient 2. Consequently, each contact interacts with a different pattern of tracks. In Patient 1, the right implant in all four contacts stimulates tracks with similar trajectories toward the frontal cortex and contacts 0 and 1 (the two most distal) show significant cerebellar components. In Patient 1, the left implant is placed within tracts that project to more inferior frontal lobe location than those in contact with the right implant. Contact 0 from the left implant lacks significant projections to the frontal lobe and instead projects toward the amygdala and temporal lobe, possibly tracing the amygdalofugal tract. In Patient 2, the most distal contacts in both leads show the same amygdala-temporal pattern as the left contact 0 from Patient 1. In Patient 2, the proximal contacts fan out toward the frontal lobe on both sides with the more proximal contacts projecting more superiorly. In these two patients, the contacts that showed the amygdala–temporal connectivity pattern (Patient 1: left contact 0; Patient 2: left and right contact 0) showed anxiety responses during programing. This suggests that in OCD, amygdalofugal involvement during DBS may be predictive of anxiety side effects (87).

At present, there is no clear consensus regarding the optimal DBS target for OCD (78–80). In the cases, we describe targeting the ALIC resulted in individual variability in the fibers passing through the DBS leads and these individual differences that may be important in surgical planning. Characterizing these connectivity differences and discovering correlates to treatment efficacy may point to a connectivity-based target independent from the current anatomical references.

CONCLUSION AND FUTURE DIRECTIONS

Precision medicine utilizes biological and other data to optimize and personalize treatment. It firmly places the individual patient at the heart of clinical practice and demands that technological developments are directed toward tailoring care to individual-specific variation. In the present paper, we highlight developments that aim to harness the power of neuroimaging for precision psychiatry. It is clear that the field is still in its infancy, and many challenges need to be addressed before the techniques described here are ready for deployment in routine clinical practice. Our quest for a better understanding of the mechanisms that lead to psychiatric disorders is essentially to find biological features that are informative in terms of diagnosis, prognosis, and treatment. Disruption in brain organization is the most proximal cause of psychiatric disorders and neuroimaging provides an invaluable tool for identifying and characterizing clinically informative features. Developments described here provide a roadmap for advancement starting from what is currently achievable.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the manuscript and approved the final version. Drs RO, BK, and WG provided data on precision targeting in patients undergoing deep brain stimulation under their care. Dr. SF provided the data and analyses for the section on supervised classification based on functional imaging data. Dr. ES provided data and conducted analyses for the section of precision mapping.

FUNDING

The study was funded by National Institute of Mental Health (R01 MH104284-01A1). The funding body had no involvement in data analysis and in the writing of this manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer ND and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Psychiatry

PERSPECTIVE
published: 28 January 2016
doi: 10.3389/fpsyt.2016.00009

Revisiting the Basic Symptom Concept: Toward Translating Risk Symptoms for Psychosis into Neurobiological Targets

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OPEN ACCESS

Edited by:
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Reviewed by:
Drozdstoy Stoyanov Stoyanov, Medical University of Plovdiv, Bulgaria
Christina Andreou, University Psychiatric Clinics Basel, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *03 December 2015*
Accepted: *14 January 2016*
Published: *28 January 2016*

Citation:
Schultze-Lutter F, Debbané M, Theodoridou A, Wood SJ, Raballo A, Michel C, Schmidt SJ, Kindler J, Ruhrmann S and Uhlhaas PJ (2016) Revisiting the Basic Symptom Concept: Toward Translating Risk Symptoms for Psychosis into Neurobiological Targets. Front. Psychiatry 7:9. doi: 10.3389/fpsyt.2016.00009

In its initial formulation, the concept of basic symptoms (BSs) integrated findings on the early symptomatic course of schizophrenia and first *in vivo* evidence of accompanying brain aberrations. It argued that the subtle subclinical disturbances in mental processes described as BSs were the most direct self-experienced expression of the underlying neurobiological aberrations of the disease. Other characteristic symptoms of psychosis (e.g., delusions and hallucinations) were conceptualized as secondary phenomena, resulting from dysfunctional beliefs and suboptimal coping styles with emerging BSs and/or concomitant stressors. While BSs can occur in many mental disorders, in particular affective disorders, a subset of perceptive and cognitive BSs appear to be specific to psychosis and are currently employed in two alternative risk criteria. However, despite their clinical recognition in the early detection of psychosis, neurobiological research on the aetiopathology of psychosis with neuroimaging methods has only just begun to consider the neural correlate of BSs. This perspective paper reviews the emerging evidence of an association between BSs and aberrant brain activation, connectivity patterns, and metabolism, and outlines promising routes for the use of BSs in aetiopathological research on psychosis.

Keywords: basic symptoms, neurobiology, psychosis, clinical high risk, aetiopathology

INTRODUCTION

Over the past two decades, preventive research in psychosis has renewed interest in subjective and subclinical psychopathology beyond positive and negative symptoms. One approach to a detailed description of such subtle disturbances, developed since the 1960s, is Huber's "basic symptoms" (BSs) concept (Figure S1 in Supplementary Material).

The Concept of Basic Symptoms

Basic symptoms are subtle, subclinical disturbances in stress tolerance, drive, affect, thinking, speech, (body) perception, motor action, and central-vegetative functions that are self-experienced with full insight into their abnormal nature (1, 2). Despite having insight, people find these subjective experiences so new and strange that they remain almost inexplicable, and therefore usually require guided questioning for their assessment. Being different from what is considered to be one's "normal" mental state, BSs remain predominately private and apparent only to the individual. Thus, rather than BSs themselves, it will be a person's affective reactions and self-initiated coping strategies in response to their BSs that may be recognized by others. Therefore, BSs differ from (secondary) negative symptoms in their current understanding as dysfunctional mental and behavioral response observable to others (3). Being experienced with full insight, BSs are also distinct from positive symptoms which are experienced by the individual as real, normal thinking, and feeling (2, 4).

Basic symptoms are an integral part of psychosis and appear throughout various stages of the disorder (Figure S1 in Supplementary Material). In combination with selected attenuated psychotic symptoms (APS), a subgroup of BSs was recently conceptualized as "self-disorders" (SDs) and a core schizophrenia vulnerability phenotype [Figures S2 and S3 in Supplementary Material (5–7)].

Basic Symptoms and Early Neurobiological Research

Huber's pioneer pneumoencephalographic *in vivo* studies on chronic schizophrenia patients with persistent negative or deficit symptoms led him to initially assume that a deficit syndrome characterized by BSs was caused in most cases by an atrophy of the basal ganglia and inherent small dysplastic lateral ventricles (8). Later on, he put emphasis on the limbic system by conceptualizing BSs as "substrate-close" or "basic," i.e., the most immediate symptomatic "expression of pathologically cerebral function in the region of the integrative system, which is responsible for the regulation of the cerebral filter and protection processes" [(9) p. 78]. While structural changes would be irreversible and potentially progressive, Huber (9) hypothesized that abnormal rhythms in EEG related to functional structures of the limbic system would only be seen in certain active (particularly early) stages.

Basic Symptoms and Risk for Psychosis

While studies in the 1980s and 1990s indicated that most BSs are indeed not specific to psychosis and may occur in other, especially non-psychotic affective disorders (4), 14 BSs were specific to the development of first-episode schizophrenia within 9.6 years (10) and employed in two clinical high risk (CHR) criteria (4, 11, 12): Cognitive Disturbances, COGDIS, Cognitive-Perceptive BSs, and COPER (**Table 1**).

A recent meta-analysis (11) revealed pooled conversion rates in COGDIS-defined samples of up to 54.9% within 4 years. Four-year conversion rates of COGDIS samples were significantly higher than those of samples established by ultra-high risk (UHR) criteria (11), mainly by APS. Thus, COGDIS is one of three criteria recommended for CHR assessment by the European Psychiatric Association (11).

TABLE 1 | CHR criteria according to the BSs concept.

Cognitive disturbances (COGDIS)
≥2 of the following 9 BSs with at least weekly occurrence (i.e., SPI-A/SPI-CY score of ≥3) within the last 3 months
• *Inability to divide attention* (B1[a]) between a (semi-)automatic and another task that strain different senses, e.g., making a sandwich (visual) while conversing (auditory)
• *Thought interference* (C2) of completely irrelevant, random thought contents
• *Thought blockages* (C3) incl. trailing off mentally and leading to a (temporary) loss of intended thought
• *Disturbance of receptive speech* (C4), i.e., a disturbance in the immediate understanding of verbal stimuli in one's mother tongue
• *Disturbance of expressive speech* (C5), i.e., in the presence of a clear idea, a disturbance in the immediate access to the adequate word in one's mother tongue
• *Thought pressure* (D3), i.e., rapid succession of irrelevant, unrelated thoughts
• *Unstable ideas of reference* (D4), experienced with immediate insight
• *Disturbances of abstract thinking* (O3), i.e., initial literal understanding of metaphoric contents or symbols
• *Captivation of attention by details of the visual field* (O7) that are random and irrelevant
Cognitive-perceptive basic symptoms (COPER)
≥1 of the following 10 BSs with at least weekly occurrence (i.e., SPI-A/SPI-CY score of ≥3) within the last 3 months and 1st occurrence ≥12 months ago (irrespective of frequency and persistence during this time)
• *Thought interference* (C2)
• *Thought blockages* (C3)
• *Disturbance of receptive speech* (C4)
• *Thought pressure* (D3)
• *Unstable ideas of reference* (D4)
• *Thought perseveration* (O1), i.e., repeated intrusion of irrelevant thought contents
• *Decreased ability to discriminate between ideas/perception, fantasy/true memories* (O2), i.e., unfounded consideration of perceptions or memories as products of current imagination
• *Derealization* (O8), incl. reduction to 2-dimensional vision and increased emotional involvement into the surrounding
• *Visual perception disturbances*, excl. blurred vision and hypersensitivity to light (D5, F2, F3, and O4), i.e., perceptive distortions that are immediately recognized as own misperceptions
• *Acoustic perception disturbances*, excl. hypersensitivity to sounds (F5 and O5), as above

[a]*Item numbers refer to the "Schizophrenia Proneness Instrument, Adult Version (SPI-A)" that gives more extended descriptions of BS and instructions for their assessment (12).*

Neurocognition and Basic Symptoms

Neurocognitive deficits are a common feature of schizophrenia and are also reported in CHR samples (13). To date, few studies

separately examined BSs samples and reported rather inconsistent findings. Generally, patients exclusively meeting BSs criteria performed intermediate to UHR patients and controls. While neurocognitive deficits and cognitive BSs did not correlate, there is some evidence for an association between exclusive presence of COPER and executive control/verbal memory dysfunction (**Table 2**) (14). Thus, BSs samples without APS or brief limited intermittent psychotic symptoms (BLIPS) exhibit fewer and less pronounced neurocognitive impairments compared to samples with APS/BLIPS. This might indicate that BSs generally precede neurocognitive impairments.

BASIC SYMPTOMS AND CURRENT NEUROBIOLOGICAL RESEARCH IN PSYCHOSIS

Neurochemistry and Basic Symptoms

Neurochemical findings suggest a role for dopaminergic, glutamatergic, serotonergic, and GABAergic systems in schizophrenia (44, 45). *In vivo* research on CHR states, defined by either UHR or BSs criteria, has focused mainly on dopamine (46, 47), glutamate (48, 49), and GABA (50, 51). Currently, the strongest evidence comes from Positron Emission Tomography studies indicating an increase of presynaptic striatal dopamine synthesis in APS patients compared with controls (46, 47). In addition, an increased dopamine synthesis capacity was also reported for individuals at genetic high risk for schizophrenia (52). Dopamine studies in BSs samples however are still missing.

These neurochemical studies have been complemented by pharmacological models of psychosis, e.g., the ketamine and endocannabinoid models (22, 23). Ketamine is an NMDA receptor antagonist, whereas cannabis or delta-9 tetrahydrocannabinol (THC) is an agonist on the cannabinoid receptor CB1. While commonly the effect of substances has to be ruled out to rate subjective experiences as BSs, recent studies ignoring this rule demonstrated an association of cannabis and ketamine use with cognitive and perceptive BSs (22, 23). Cannabis-using CHR patients had more BSs than non-using patients (22), while non-CHR cannabis users had significantly more positive, disorganization, general symptoms and BSs and also more neurocognitive deficits than non-users (23). Furthermore, the profiles of BSs and neurocognitive deficits of high-potency cannabis and ketamine users resembled COPER patients who subsequently converted to psychosis more closely than the profiles of users of other substances (23). Additional support of an association between the endocannabinoid system and BSs comes from one study investigating anandamide a bioactive lipid binding to cannabinoid receptors, in the cerebrospinal fluid (CSF) of CHR states (24). CHR individuals with higher anandamide levels showed a lower risk for transitioning to psychosis. Finally, one study of the metabolic profile in CSF (25) reported increased levels of glucose and VGF peptide (a polypeptide expressed by neurons and neuroendocrine tissues), and decreased levels of lactate and transthyretin protein in CHR patients (**Table 2**).

Electrophysiology and Basic Symptoms

EEG and magnetoencephalographic (MEG) recordings permit the non-invasive assessment of electric currents of large populations of neurons, thus providing an estimate of both spontaneous and task-induced activity with millisecond resolution.

In a study of event-related potentials (ERP: P100, N170, and N250) using a facial recognition paradigm (26), emotion recognition was reduced in CHR groups and accompanied by a decrease in ERP amplitudes. As emotion recognition is already completed within 100 msec (53), these findings may reflect more complex perceptual processes. Further research on their relation to visual BSs may be promising. Moreover, reduced P300 amplitudes during an auditory oddball paradigm were found in a CHR sample (27). The COPER group showed a significant lower amplitude at a left temporoparietal site, whereas the APS/BLIPS group elicited smaller amplitudes at midline and left hemispheric electrode sites. These findings suggest potential differences in ERPs between BSs-defined and APS-defined CHR patients that might be related to different states of disturbed information processing.

In addition, Arnfred et al. (28) examined correlations between proprioceptively evoked event-related responses and changes in SDs in a small sample of schizophrenia patients. EEG data were examined for the spectral power of evoked-activity at beta/gamma-band frequencies (13–80 Hz) in response to a sudden change in muscle contraction. Increased total scores as well as increased ratings in the subscales "cognition and stream of consciousness," "self-awareness and presence" and "bodily experiences" correlated significantly with lower gamma-band activity over parietal electrodes and higher peak frequencies in beta-activity (**Table 2**). Beside task-related activity, resting-state neural oscillations have also been recently investigated in CHR samples defined by both APS and BSs (31, 32), indicating increased delta/theta-band activity with reduced alpha-band power (31) and reduced theta-band activity which correlated with neurocognitive impairments (32), respectively. Moreover, there is emerging evidence that spontaneous gamma-band activity may differentiate CHR patients from controls (33).

These findings provide preliminary evidence for a potential link between BSs and abnormalities in EEG parameters in patients with schizophrenia and CHR groups. However, it is essential for these findings to be replicated and expanded in large samples. Overall, data on aberrant neural oscillations and ERP-parameters are consistent with data from APS-only (54) and schizophrenia samples (55), suggesting a continuum between psychosis-risk and progression to ScZ. Thus, neural oscillations and their synchronization could constitute a candidate mechanism for BSs. During normal brain functioning, rhythmic activity, especially at gamma-frequency ranges, are important for ensuring effective communication between and within neuronal assembles and correlate with a range of cognitive processes, including attention, perception, and working memory (55). Moreover, 30–80 Hz activity is generated by the interplay between GABAergic-interneurons and excitatory drive mediated through NMDA/AMPA-receptors (56, 57). These cellular mechanisms have been shown to be disrupted in schizophrenia (58).

TABLE 2 | Summary of neurobiological studies of basic symptoms.

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
NEUROCOGNITIVE STUDIES				
Pukrop et al. (15)	Aim: identifying potential biobehavioral risk factors and investigate illness progression within a cross-sectional design Hypothesis: continuous decline of neurocognitive functioning in scope and intensity from COPER/GRFD and APS/BLIPS to FEP and MEP	Sample: COPER/GRFD (n = 38), APS/BLIPS (n = 90), FEP (n = 86), MEP (n = 88) Assessments: BSABS, SIPS/SOPS; neurocognitive tests (VBM, CPT-IP, DRT, AVLT, ROFT, WCST, and verbal fluency	COPER/GRFD > APS/BLIPS > FEP > MEP COPER/GRFD had abnormalities in verbal memory (immediate recall) and verbal executive function (verbal fluency)	Results support a neurodevelopmental model of psychosis with further progressive mechanisms and are consistent with a primary involvement of left frontotemporal networks in the prodromal phase
Simon et al. (16)	Aim: better understanding of cognitive functioning and its course in CHR states of psychosis Hypotheses: (1) patients with BSs show cognitive impairment when compared with normative values and PCo and (2) these deficits are comparable to those observed in patients meeting UHR criteria	Sample: BS (n = 24), UHR (n = 69), FEP (n = 43), PCo (n = 49) Assessments: SPI-A, SIPS/SOPS; neurocognitive tests (MWT, LNS, TMT, verbal fluency, WCST, AVLT, and TAP)	BSs patients worse compared with normative data (working memory, verbal fluency), but not compared to PCo BS > UHR	Most pronounced deficits affect executive functions and working memory → frontal lobe dysfunction in CHR groups
Schultze-Lutter et al. (17)	Aim: possible association between subjective and objective cognitive disturbances and their relation to different CHR states Hypotheses: COPER/GRFD less impaired than APS/BLIPS; Association between subjective and objective cognitive disturbances	Sample: COPER/GRFD (n = 33), APS/BLIPS (n = 69) Assessments: BSABS/SPI-A, SIPS/SOPS; neurocognitive tests (VBM, CPT-IP, DRT, LNS, SOPT, AVLT, ROFT, TMT, DST, WCST, and verbal fluency)	COPER/GRFD > APS/BLIPS Association between subjectively reduced stress tolerance and processing speed No further correlation between subjective cognitive–perceptive disturbances and performance in neurocognitive tests	Results support earlier findings showing lack of association between neurocognitive deficits and psychopathologic features. Possible additional predictive power of neurocognitive deficits in CHR states
Frommann et al. (14)	Aim: addressing the neurocognitive functions of 2 different CHR groups in comparison to a healthy control group Hypotheses: (1) CHR have generalized neurocognitive deficits compared with HC, (2) Measures of executive function and verbal memory are more impaired than those of other domains in the APS/BLIPS, and (3) Individuals in an COPER/GRFD are intermediate between HC and APS/BLIPS	Sample: COPER/GRFD (n = 116), APS/BLIPS (n = 89), HC (n = 87) Assessments: ERIraos; neurocognitive tests (MWT, CPT-IP, LNS, SOPT, AVLT, TMT, DST, and verbal fluency)	HC > COPER/GRFD > APS/BLIPS In COPER/GRFD executive control was significantly more impaired in comparison to the remaining domains. In the APS/BLIPS the verbal memory domain was more impaired in comparison to the remaining domains	Executive control seems to be compromised in the COPER/GRFD (prior to the onset of positive symptoms), whereas verbal memory dysfunctions appear to evolve during a later prodromal stage
Simon et al. (18) [follow-up of Simon et al. (16)]	Aim: long-term follow-up of CHR individuals and their cognitive performance. Comparing individuals who later convert to psychosis with those who do not convert to psychosis Hypotheses: BSs individuals are less cognitively impaired than UHR individuals. UHR individuals that remit from an initial UHR status show cognitive impairment that is at intermediate position between BSs and non-remitting or converting UHR individuals	Sample: BS (n = 26), UHR_{rem} (n = 35), $UHR_{n\text{-}rem}$ = 19, FEP (n = 48), PCo (n = 49) Assessments: SPIA, SIPS/SOPS; neurocognitive tests (MWT, LNS, TMT, verbal fluency, WCST, AVLT, and TAP)	At baseline, global cognitive functioning showed an increase of impairment from PCo to FEP (mean sum score of cognitive functioning: PCo > BS > UHR_{rem} > $_{UHRn\text{-}rem}$ > FEP) At baseline BS group was impaired, but less than UHR group (verbal memory, verbal fluency, executive functions)	Even in the absence of psychotic symptoms cognitive functioning, including executive functioning, was impaired in this CHR sample, this calls for strong efforts to address and remediate cognitive impairments as early as possible in CHR patients

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Koutsouleris et al. (19)	Aim: can multivariate neurocognitive pattern classification facilitate the diagnostic identification of different CHR states for psychosis and facilitate an individualized prediction of illness transition Hypotheses: (1) the employment of a support vector machine in conjunction with ensemble learning methods facilitates recognition of different CHR states and the prediction of frank psychosis. (2) Potentially complex patterns of cognitive ability derived from the combination of several neuropsychological tests may also facilitate the individualized prediction	Sample: HC (n = 30), COPER/GRFD (n = 20), APS/BLIPS (n = 28) Assessments: BSABS, CAARMS; neurocognitive tests (MWT, LNS, SOPT, DS, AVLT, TMT, DST, and verbal fluency)	COPER/GRFD patients performed worse in spatial working memory (SOPT) and, processing speed (TMT-A) and executive functions (TMT-B) compared to HC The discriminative pattern of HC vs. COPER/GRFD showed high selection probabilities (>90%) in the working memory and verbal learning/memory domain	The binary classification results suggest that a pattern of altered verbal and mnemonic functions may reliably distinguish CHR individuals experiencing predictive basic symptoms from healthy controls
Haug et al. (20)	Aim: explore the relationships between SDs, as measured by the EASE, and neurocognitive test performance in the early phase of schizophrenia Hypothesis: there are some associations between SDs and neurocognitive deficits, and that higher SDs would correlate with poorer neurocognitive performance	Sample: SZ (n = 57) Assessments: EASE; neurocognitive tests (DST, LNS, Logical Memory Test of WMS, ROFT, and DKEFS)	EASE total score was significantly associated with verbal memory (high levels of SDs were associated with impaired verbal memory) No association with SDs and working memory, executive function or psychomotor speed	General lack of associations between SDs and neurocognition is that SDs and these specific neurocognitive functions could represent different basic expressions of the illness Neurocognitive test situation is structured with little affective and somatosensory salience. In contrast, the questions asked in the EASE have focus on more subjective experiences in everyday situations where somatosensory and affective processes interact with neurocognition
Nordgaard et al. (21)	Aim: explore potential associations between SDs, neurocognitive performance, rationality and IQ in patients with schizophrenia Hypothesis: there are some associations between SDs and neurocognitive performance	Sample: SZ (n = 31) Assessments: EASE; neurocognitive tests (subtests from the Cambridge Neuropsychological Test Automated Battery)	No significant correlation was found between SDs and neurocognitive performance SDs correlate significantly with rationality (tested with syllogism test)	The general lack of associations between SDs and neurocognitive performance suggests that these phenomena represent different aspects of the disorder – i.e., SDs seem to reflect aspects that are essential or specific to schizophrenia, whereas impaired neurocognitive performance does not The association between rationality and SDs could signify, that high levels of SDs make the patient insensitive to detect violations of logic
NEUROCHEMICAL AND DRUG STUDIES				
Korver et al. (22)	Aim: investigation of the relationship between cannabis use, UHR symptoms and neuropsychology Hypothesis: Cannabis-using control subjects and UHR subjects show increased symptomatology and reduced neuropsychological functioning compared to non-using subjects	Sample: UHR subjects (n = 63, of them 34 cannabis users), HC (n = 58, of them = 28 cannabis users) Assessments: SIPS, BSABS-P, CIDI (sections J and L); neurocognitive tests (FTT, CPT, CVLT, National Adult Reading Test, and verbal fluency)	More basic symptoms and UHR symptoms in cannabis-using UHR subjects compared to non-using UHR subjects Cannabis-using control group showed more subclinical UHR, basic symptoms and more dysfunction than non-cannabis control subjects Frequency of cannabis use correlated with severity of several UHR symptoms No significant relationship between frequency of cannabis use and any neuropsychological test.	The association between frequency of cannabis use and UHR symptoms led to the assumption that frequent use of cannabis is related to changes in visual information processing Frequent use of cannabis could represent a risk factor for developing subclinical UHR symptoms and impaired neurocognitive functioning in healthy subjects

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Morgan et al. (23)	Aim: (1) Assess the degree of basic symptoms in currently non-psychotic users of 3 classes of drugs, namely cannabis (high-potency cannabis), stimulants (cocain) and dissociative anesthetics (ketamine). (2) Investigate measures that have shown sensitivity to cognitive deficits in prodromal individuals Hypothesis: are BSs and neurocognitive deficits present in individuals dependent on these drugs? Are BSs associated with drug use *per se* or do users of these different pharmacological agents display differing profiles?	Sample: *N* = 130; dependent high-potency cannabis users (*n* = 29), dependent cocaine users (*n* = 22), dependent ketamine users (*n* = 21), recreational drug users (*n* = 28), drug-naïve control (*n* = 30) Assessments: SPI-A; neurocognitive tests (RBMT and STW)	Deficits in working memory were only found in ketamine users and deficits in frontal functioning in ketamine and high-potency cannabis users. Long-term memory was impaired in all drug users The symptom profile associated with chronic ketamine use was similar to individuals with basic symptoms who subsequently make a transition to psychosis	Ketamine, high-potency cannabis and cocaine users showed basic symptoms, whereas ketamine users exhibited highest levels of basic symptoms The existence of basic symptom-like phenomena is a potential mechanism by which heavy drug use triggers acute psychosis in vulnerable individuals
Koethe et al. (24)	Aim: to evaluate whether changes in the endocannabinoid system [i.e., Anandamide in cerebrospinal fluid (CSF)] are detectable in initial prodromal states of psychosis Hypothesis: elevation of Anandamide in CSF is apparent in early stages of psychosis	Sample: HC (*n* = 81), UHR (*n* = 27) Assessments: SPI-A, PANSS, SOPS	Cerebrospinal Anandamide levels in patients were significantly elevated. Patients with lower levels showed a higher risk for transiting to psychosis earlier	The up-regulation of Anandamide in the initial prodromal course suggests a protective role of the endocannabinoid system in early schizophrenia
Huang et al. (25)	Aim: to evaluate whether CSF alterations of glucose, lactate, VGF and transthyretin, that have been found in SZ, are already detectable in UHR Hypothesis: none stated	Sample: FEP, drug naive (*n* = 54); UHR (*n* = 24); HC (*n* = 70) Assessments: SPI-A, PANSS, SIPS/SOPS	~1/3 of UHR patients displayed proteomic/metabolic profiles characteristic of FEP, drug naive, i.e., changes in levels of glucose, lactate, VGF-derived peptide (VGF23-62) and transthyretin	Schizophrenia-related biochemical disease processes can be traced in CSF of prodromal patients
ELECTROPHYSIOLOGICAL STUDIES				
Wölwer et al. (26)	Aim: to investigate impairments of facial affect recognition and its neurophysiological correlates in two different CHR states Hypothesis: CHR individuals show poorer affect recognition performance and abnormalities in ERP components as correlates of impaired encoding of facial features and affect decoding processes	Sample: HC (*n* = 32), COPER/GRFD (*n* = 16), APS/BLIPS (*n* = 21) Assessments: ERIraos Pictures of Facial Affect (6 basic emotions) EEG: event-related potentials (ERP: P100, N170, N250)	Facial affect recognition in CHR < HC, no significant difference between CHR groups Amplitudes of all three ERPs in CHR < HC (CHR groups were collapsed for ERP analysis)	(1) The ability to discriminate emotional expressions in faces is impaired in the CHR state (COPER/GRFD as well as APS/BLIPS), demonstrating an impairment of social cognition already before the first psychotic episode (2) Reduced N100 may be due to an impairment of fundamental visual processes, N170 may reflect dysfunctions in visual processing of facial structures. Diminished N250 amplitudes may indicate difficulties to associate the structural representation of the face with semantic and contextual information

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Frommann et al. (27)	Aim: to determine whether individuals in two different CHR states show P300 amplitude reductions and altered topography Hypothesis: CHR individuals in both states show left temporoparietal amplitude reduction compared to controls	Sample: HC (n = 40), COPER/GRFD (n = 50), APS/BLIPS (n = 50) Assessments: ERIraos EEG: ERP P300, oddball paradigm	Hit rate: APS/BLIPS = HC, COPER/GRFD = HC* P300 latency: APS/BLIPS = HC, COPER/GRFD = HC* *COPER/GRFD vs. APS/BLIPS not reported P300 amplitude: sagittal midline (SM) and left hemisphere electrodes: APS/BLIPS < HC, COPER/GRFD = HC, APS/BLIPS = COPER/GRFD Sagittal midline: BLIPS positive < BLIPS negative Left temporoparietal electrode: COPER/GRFD < HC	P300 activity in the COPER/GRFD differed only at left temporoparietal position from HC, whereas in the APS/BLIPS, markedly amplitude reductions were observed, pronounced over the left hemisphere Findings may indicate a disturbance of neural generators in the left superior temporal lobe occurring early in the disease process. Temporoparietal P3 reductions may indicate vulnerability to psychosis. Sagittal midline P3 amplitudes may reflect changes underlying the development of psychotic symptoms
Arnfred et al. (28)	Aim: explore potential associations between SDs and abnormalities of early contralateral proprioceptive evoked oscillatory brain activity Hypothesis: none stated	Sample: SZ (n = 12) Assessments: EASE EEG: proprioceptive-evoked potentials	Higher EASE scores (i.e., increased SDs) were associated with lower peak parietal gamma frequencies and higher peak beta amplitudes over frontal and parietal electrodes in the left hemisphere following right-hand proprioceptive stimulation	SDs may be associated with dysfunction of early phases of somatosensory processing
Sestito et al. (29)	Aim: to investigate the relation between SDs and subtle, schizophrenia-specific impairments of emotional resonance that are supposed to reflect abnormalities in the mirror neurons mechanism. To test whether electromyographic response to emotional stimuli (i.e., a proxy for subtle changes in facial mimicry and related motor resonance mechanisms) would predict the occurrence of anomalous subjective experiences (i.e., SDs) Hypothesis: none stated	Sample: SZ spectrum (n = 18) Assessments: BSABS EMG: multimodal paradigm, recording facial electromyographic activity of muscles in response to positive and negative emotional stimuli	SZ spectrum patients showed an imbalance in emotional motor resonance with a selective bias toward negative stimuli, as well as a multisensory integration impairment. Multiple regression analysis showed that electromyographic facial reactions in response to negative stimuli presented in auditory modality specifically and strongly correlated with SDs subscore	The study confirms the potential of SDs as target phenotype for neurobiological research and encourages research into disturbed motor/emotional resonance as possible body-level correlate of disturbed subjective experiences in SZ spectrum
Sestito et al. (30)	Aim: to explore whether a low or high emotional motor resonance occurring in SZ spectrum relates to clinical features and BSs Hypothesis: none stated	Sample: SZ spectrum (n = 19) Assessments: BSABS EMG: multimodal paradigm, recording facial electromyographic activity of muscles in response to positive and negative emotional stimuli	SZ spectrum patients more resonating with negative emotional stimuli (i.e., externalizers) had significantly higher scores in BSABS Cluster 3 (vulnerability) and more psychotic episodes than internalizers patients. SzSp patients more resonating with positive emotional stimuli (i.e., externalizers) scored higher in BSABS Cluster 5 (interpersonal irritation) than internalizers	Abnormal subjective experiences are related to low-level emotional motor mechanisms disruption, indexed by electromyographic facial reactions
Van Tricht et al. (31)	Aim: quantitative EEG spectral power and alpha peak frequencies (APF) were determined in CHR subjects Hypothesis: none stated	Sample: CHR (n = 113), HC (n = 25) Assessments: SPI-A, SIPS/SOPS EEG: Ag/AgCl electrodes were applied according to the international 10–20 system; individual APF were assessed	Compared to CHR without transition HC, CHR with transition showed higher theta and delta on frontal and central scalp locations and lower occipital-parietal APF. Furthermore, in CHR without transition, upper parietal alpha was lower compared to HC. A model for prediction of psychosis included frontal theta and delta as well as the APF as predictors of 18-month conversion rates	Theta and delta ranges and APF can contribute to the short-term prediction of a first psychotic episode

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Andreou et al. (32)	Aim: investigate EEG resting-state connectivity in CHR compared to SZ spectrum and HC, and its association with cognitive deficits Hypothesis: none stated	Sample: CHR (n = 28), SZ spectrum (n = 16), HC (n = 23) Assessments: SPI-A, SIPS/SOPS; Neurocognitive tests (VLMT, WMS, TMT, LNS, DS, DST, verbal fluency) EEG: 64-channel resting state EEG recordings (eyes closed).	SZ displayed increased theta-band resting-state multivariate interaction measure connectivity across midline, sensorimotor, orbitofrontal regions and the left temporoparietal junction. CHR displayed intermediate theta-band connectivity patterns that did not differ from either SZ or HC: mean theta-band connectivity within the above network partially mediated verbal memory deficits in SZ and CHR	Aberrant theta-band connectivity may represent a trait characteristic of schizophrenia associated with neurocognitive deficits
Ramyead et al. (33)	Aims: to assess whether abnormalities in current source density (CSD) and lagged phase synchronization of oscillations across distributed regions of the brain already occur in patients with CHR state for psychosis Hypotheses: (1) CHR with transition would demonstrate abnormal CSD in both the high gamma and beta frequency bands when compared with CHR without transition and HC. (2) The lagged phase synchronization of beta, the long-range modulator, would be more decreased in CHR with transition compared to CHR without transition and HC as a function of increasing Euclidian distance	Sample: CHR (n = 63), HC (n = 29) Assessments: BSIP; neurocognitive tests (TAP) EEG: resting-state EEG	CHR with transition showed higher gamma activity in the medial prefrontal cortex compared to HC, which was associated with abstract reasoning abilities in CHR with transition. Furthermore, in CHR with transition lagged phase synchronization of beta oscillations decreased more over Euclidian distance compared to CHR without transition and HC. Finally, this steep spatial decrease of phase synchronicity was most pronounced in CHR with transition patients with high positive and negative symptoms scores	Patients who will later make the transition to psychosis are characterized by impairments in localized and synchronized neural oscillations providing new insights into the pathophysiological mechanisms of schizophrenic psychoses and may be used to improve the prediction of psychosis
IMAGING STUDIES: STRUCTURAL				
Hurlemann et al. (34)	Aims: to which extent interrelated structural–functional deficits of the hippocampus reflect a vulnerability to schizophrenia? Hypothesis: hippocampal volume reduction should be paralleled by a progressive worsening of verbal learning and memory	Sample: COPER/GRFD (n = 20), APS/BLIPS (n = 16), HC (n = 30) Assessments: ERIraos; neurocognitive tests (MWT and AVLT)	Hippocampal volume decrease in COPER/GRFD of 7.7% In APS/BLIPS but not in COPER/GRFD, a 9.2% deficit in AVLT (delayed recall) was correlated with reduced MRI hippocampal volumes	Progressive and interrelated structural–functional pathology of the hippocampus could be an index of increased risk for schizophrenia
Koutsouleris et al. (35)	Aims: (1) to investigate structural brain differences between participants with COPER/GRFD or APS/BLIPS. (2) To examine associations between structural differences and later disease conversion Hypothesis: no hypothesis stated	Sample: COPER/GRFD (n = 20), APS/BLIPS (n = 26), HC (n = 75); 4-year follow-up (total n = 33; 13 for COPER/GRFD and 20 for APS/BLIPS), 15 transitioned to psychosis [COPER/GRFD (n = 1), APS/BLIPS (n = 14)]	Gray matter reductions (controls > COPER/GRFD) in fusiform, superior, middle and inferior temporal gyri, as well as amygdala and hippocampus, bilaterally. For COPER/GRFD > APS/BLIPS, differences in frontal clusters in left subgenual anterior cingulate cortex as well as in the ventromedial prefrontal cortex and dorsomedial prefrontal cortex, bilaterally	BSs are associated with medial and lateral temporal lobe abnormalities, as well as subtle perisylvian, prefrontal, parietal, thalamic and cerebellar anomalies; APS/BLIPS mark are characterized by more pronounced structural anomalies within these regions
Koutsouleris et al. (36)	Aims: to investigate the ability of support vector machines (SVMs) to detect different CHR states by performing a classification of HC vs. individuals with CHR (grouped into COPER/GRFD and APS/BLIPS) and to further evaluate SVMs' performance in predicting transition in the CHR converting to clinical disorders Hypothesis: None stated	Sample: COPER/GRFD (n = 20), APS/BLIPS (n = 25), HC (n = 25); follow-up 13 for COPER/GRFD, and 20 for APS/BLIPS, 15 transitioned to psychosis [COPER GRFD (n = 1), APS/BLIPS (n = 14)]	Multivariate neuroanatomical pattern classification can accurately discriminate between COPER/GRFD, APS/BLIPS, and HC. COPER/GRFD patterns appear be distinguishable from HC on the basis of gray matter patterns of both augmentations and reductions in temporal lobe regions. They differ from APS/BLIPS on the basis of gray matter patterns around the cingulate cortex and the perisylvian fissure	COPER/GRFD without other CHR criteria, appear to be distinguishable from both HC and APS/BLIPS subgroups; however, the pattern linked to conversion is not as clear in COPER/GRFD as it is in APS/BLIPS. This is partly due to the fact that a very low proportion of COPER/GRFD patients converted to psychosis (1 on 20) in this study

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Koutsouleris et al. (37)	Aims: to test the "accelerated aging" hypothesis across different psychiatric disorders, using brain age gap estimations; to employ multivariate pattern analysis (MPVA) to estimate classifiers' ability to distinguish between different pathologies Hypothesis: no hypothesis stated	Sample: COPER/GRFD (n = 21), APS/BLIPS (n = 68), major depression (n = 104), borderline personality disorder (n = 57), SZ (n = 141), HC (n = 437)	Results yield negative brainage effects in the COPER/GRFD group	It appears that the COPER/GRFD group showed "decelerated brain aging"; the authors suggest this effect could be due to a maturational delay mechanism, or a compensatory neural mechanism at the early stage of the disease
Tepest et al. (38)	Aims: to investigate interhemispheric connectivity, using measures of the corpus callosum (CC); to investigate corticocortical connectivity, using a gyrification index (GI) measure Hypotheses: changes in both measures reflecting impairments in long distance as well as in short distance connectivity, in comparison with HC subjects	Sample: CHR (n = 21), SZ (n = 21), HC (n = 21)	GI frontal region SZ > HC (+20%) SZ > CHR (+9%) CHR > HC (+10%) GI parietal region SZ > HC (+15%) SZ > CHR (+8%) CHR > HC (+7%)	Results suggest an impairment in short-range corticocortical connectivity, whereas no impaired long-range connectivity no difference in CC measurements
IMAGING STUDIES: FUNCTIONAl				
Ebisch et al. (39)	Aims: do FEP patients show functional activation abnormalities during social perception of other individuals' affective tactile stimulation? Hypothesis: none stated	Sample: FEP (n = 24), HC (n = 22) Assessments: SPI-A, PANSS fMRI: social perception task using videos depicting animate/inanimate individuals using tactile stimulation	Ventral premotor cortex activation negatively correlates with SPI-A basic symptom scores (0–150)	Results likely reflect poor multisensory integration in the vPMC (visual, tactile, proprioceptive self-experiences)
Ebisch et al. (40)	Aims: investigate connectivity underlying the link between aberrant self-experience and social cognition in FEP Hypothesis: none stated	Sample: FEP (n = 24), HC (n = 22) Assessments: SPI-A, PANSS fMRI: social perception task using videos depicting animate/inanimate individuals using tactile stimulation	Connectivity between ventral premotor cortex and posterior cingulate cortex correlates with SPI-A basic symptom scores (0–150)	Increased functional coupling between antagonistic functional networks may alter functional segregation, thereby disturbing the relationship between the intrinsic (self-referential) and extrinsic (interacting) self
Wotruba et al. (41)	Aims: to examine whether salience network (SN) disturbances can be evidenced in CHR. Furthermore, to explore if within and between intrinsic functional connectivity in the SN, default mode network (DMN) and task-positive network (TPN) are associated to symptoms related to reality distortions and cognitive processing in CHR subjects Hypothesis: clinical symptoms and disturbances of cognition seen in CHR subjects are reflected by an aberrant spatial extent in DMN, TPN, and SN, accompanied by a loss of anticorrelation between those 3 networks	Sample: BS (n = 28), UHR (n = 19), HC (n = 29) fMRI: resting-state paradigm	mPFC–rDLPFC connectivity, as well as rAI-PCC connectivity increased in BSs and UHR vs. HC (anticorrelated for controls). Significant anticorrelation between the task-positive network (bilateral fronto-parietal) and DMN for HC, but not CHR groups	Absence of typical anticorrelated patterns may relate to irregularities in discrimination between external and internal sources of information, thereby potentially leading to risk symptoms. Note however that no significant differences were found between BSs risk and UHR (UHR seems to show trend-like increased connectivity in rAI-PCC)

(Continued)

TABLE 2 | Continued

Study	Aims and hypotheses	Sample and assessments	Main results	Discussion and conclusion
Wotruba et al. (42)	Aims: explore functional brain correlates during both anticipation and receipt of rewards and to evaluate their association with symptoms in unmedicated persons at risk for psychosis Hypotheses: (1) positive symptoms are associated with activation of the ventral striatum (VS) and the anterior insula during reward anticipation, (2) negative symptoms are associated with reduced VS activation during reward anticipation, and (3) depressive symptoms are associated with reduced VS and mOFC activation during processing of rewarding outcomes	Sample: CHR (n = 21) meeting UHR + BS criteria, HC (n = 24) fMRI: monetary incentive delay task to probe neural responses for reward anticipation and receipt	During reward anticipation, increased in CHR: PCC, SFG, medial frontal gyrus. No correlations with BSs, but with SIPS positive in ventral striatum and rAI (positive correlation) No group differences for receipt of reward contrast, correlations with psychopathology: left ventral striatum with negative symptoms (negative correlation)	Evidence for dysregulation of reward processing in risk period, with frontal compensation. Higher striatal activation might be linked to "increased salience" hypothesis in early stages
Ferri et al. (43)	Aim: to examine embodied simulation as driven by mirror neuron in schizophrenia Hypothesis: none stated	Sample: SZ (n = 22), HC (n = 22) fMRI: goal-related actions in either a neutral or emotional context	Lower activation of the left inferior parietal lobule when observing neutral action correlated with increased basic symptoms score	Emotional cues might allow SZ patients to recover mirror neuron-driven embodied simulation at least in part. However, their understanding of the emotional components of others' actions will likely remain deficient

SPI-A, Schizophrenia Proneness Instrument, Adult version; SPI-CY, Schizophrenia Proneness Instrument, Child and Youth version; BSABS, Bonn Scale for the Assessment of Basic Symptoms; EASE, Examination of Anomalous Self-Experience; ERIraos, Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia; SIPS/SOPS, Structured Interview for Prodromal Syndromes; CAARMS, Comprehensive Assessment of At Risk Mental States; CHR, clinical high risk; BSs, basic symptoms; SDs, self-disturbances; UHR, ultra-high risk; FEP, first-episode psychosis; MEP, multiple episode psychosis; SZ, schizophrenia; PCo, patient controls; HC, healthy controls.

Neurocognitive tests: MWT, Mehrfach–Wortschatz-Test; CPT-IP, Continuous Performance Test-Identical Pairs version; TAP, Testbatterie zur Aufmerksamkeitsprüfung; DRT, Delayed Response Task; LNS, Letter-Number Span; DS, Digit Span Test; SOPT, Subject Ordered Pointing Task; AVLT, Rey Auditory Verbal Learning Test; ROFT, Rey–Osterrieth Complex Figure Test; WMS, Wechsler Memory Scale; TMT, Trail-Making Tests; DST, Digit Symbol Test; WCST, Wisconsin Card Sorting Test; RBMT, Rivermead Behavioural Memory Test; STW, Spot The Word Test; FTT, Finger-Tapping Test; CVLT, California Verbal Learning Test.

Neuroimaging: vPMC, ventral premotor cortex; mPFC, medial prefrontal cortex; rDLPFC, right dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; rAI, right anterior insula; SFG, superior frontal gyrus; mOFC, medial orbitofrontal cortex.

Functional and Structural Imaging and Basic Symptoms

To date, a handful of magnetic resonance imaging (MRI) studies have included the assessment of BSs by specialized instruments (**Table 2**). Their findings were similar to those reported for UHR and schizophrenia patients (59–61).

Structural Studies

Five studies have investigated structural characteristics in relation to BSs. These studies distinguished "early risk" for psychosis, characterized by either COPER or the UHR genetic risk criterion (GRFD) in the absence of symptomatic UHR states, from "late risk," which encompasses individuals meeting APS or BLIPS criteria, irrespective of the presence of BSs (34–37). Hurlemann et al. (34) reported bilaterally reduced hippocampi in COPER/GRFD and in APS/BLIPS subjects, correlating in the latter group with delayed recall in a verbal memory test. Koutsouleris et al. (35) employed voxel-based morphometry analyses to examine morphological differences between early- and late-risk samples. In comparison to controls, the COPER/GRFD group presented gray matter reductions involving the fusiform, superior, middle, and inferior temporal gyri, as well as amygdala and hippocampus, bilaterally. While they were associated with medial and lateral temporal lobe abnormalities, as well as subtle perisylvian, prefrontal, parietal, thalamic, and cerebellar anomalies, these alterations were continuous with late-risk participants (35). In a parallel study using multivariate neuroanatomical pattern classification, morphological patterns of COPER/GRFD were distinguishable from controls on the basis of gray matter patterns of both augmentations and reductions in temporal lobe regions; they differed from late risk on the basis of gray matter patterns covering the anteroposterior cingulate cortex and the perisylvian fissure (36). Using brain age gap estimations, the same group of participants reporting COPER/GRFD presented a "decelerated brain aging," suggesting differential maturational dynamics at different stages of risk. Such deceleration could be due to a maturational delay mechanism, or a compensatory neural mechanism at the early stage of the disease (37). A further study indicated increased gyrification in frontal and parietal regions in BSs individuals (identified using COGDIS) compared to controls, implicating impaired short-range corticocortical connectivity (38).

Functional Imaging Studies

To date, only five fMRI studies have examined BSs (39–43). Studies examining cerebral activation in patients with schizophrenia consistently reported significant associations between BSs and localized decreased activations in the ventral premotor cortex (40) and in the left inferior parietal lobule during passive viewing of neutral actions (43). Notably, increased connectivity between ventral premotor cortex and posterior cingulate cortex was associated with the severity of BSs in first-episode schizophrenia patients (39). This is consistent with another study examining the relationship between task positive and default-mode connectivity in CHR subjects, which reported a lack of anticorrelation between task positive and task negative networks (41).

The preliminary nature of these studies does not enable any definite conclusion as to the links between altered functional connectivity and BSs. Differences in methodology as well as heterogeneity of samples, which included both CHR and frankly psychotic patients, limit the interpretation of the available results and likely contributed to their inconsistencies (62). Furthermore, the variety of BSs involved, which touch upon motivation, cognitive and perceptual domains are likely to involve a variety cortical regions and networks. Overall, these pioneering studies suggest atypical patterns of neural activation in relation to BSs in terms of both reduced activity in discrete regions associated to self-other boundary distinction and atypical cross-talk between networks, which is similar to what is observed in UHR populations (59).

DISCUSSION AND PERSPECTIVES

Current Evidence

Although, in their original formulation, BSs were thought to reflect core abnormalities in brain functioning, investigations have only recently begun to look for their neurobiological origins, especially in CHR groups. Given the importance of BSs criteria in CHR research (11), further studies are needed to provide more detailed insights into the underlying neurobiological correlates that give rise to self-experienced disturbances in perception and cognition. Such candidate mechanisms could be of crucial importance for understanding the etiology of psychosis-risk as well as provide potential biomarkers for early detection and diagnosis. Moreover, such insights could point toward useful targets for novel pharmacological and psychological interventions that might ultimately reduce conversion rates.

Future Studies into the Neurobiology of Basic Symptoms

Current studies provide only preliminary evidence for neurobiological mechanisms underlying BSs. Available data highlights that diverse anatomical, pharmacological and functional correlates may be involved in the manifestation of BSs in psychotic and CHR individuals. These include structural alterations, changes in ERPs and neural oscillations, neurotransmitter systems as well as evidence for changes in large-scale networks as assessed with fMRI. For more detailed and possibly mechanistic insights into neurobiology of BSs, different strategies need to be employed.

First, BSs in their original formulation are a heterogeneous set of symptoms comprising disturbances in perception, affect, drive, and cognition. Dimensional analyses of BSs indicated six BSs dimensions in adult psychosis patients that appear stable across various states of the illness [i.e., from the prodromal phase via the first episode to chronic states/relapse (4, 63)]. However, these six dimensions could not be replicated in a sample of early-onset schizophrenia patients, where four slightly different dimensions emerged [Figures S4–S6 and Table S1 in Supplementary Material (4)]. Thus, while past studies have either considered BSs in total (e.g., SPI-A sum score) or only considered COPER or COGDIS, BSs dimensions or even more differentiated BSs cluster (e.g., distinguishing even further between cognitive, speech, visual, and acoustic disturbances) might offer a more appropriate route to detecting neurobiological mechanisms underlying (if related to specific BSs)

or further promoting (if related to unspecific BSs) development of psychosis. Furthermore, as recently indicated for single attenuated and manifest psychotic "Ich-Störungen (64), even investigating the neurobiology of single BSs may provide some significant insight. For example, when considering subjective disturbances of receptive and expressive speech as subtle, functional and only transient variants of receptive and amnesic aphasia, respectively (65), on a phenomenological level, it seems promising to investigate the role of brain regions which are highly correlated with theses neurologic syndromes also in patients exhibiting these BS.

Further insights into the origins of BSs may be derived from considering their developmental pattern and relationship to brain development. Psychoses, in particular of the schizophrenia-spectrum, are considered a fundamentally neurodevelopmental disorder involving two critical time windows [early (perinatal) brain development and adolescence] that together produce the symptomatic manifestations of the disorder. In this framework, early developmental insults may lead to dysfunction of specific neural networks that would account for early and (in some cases) trait-like signs and symptoms, which may have little or no clinical significance. The development of a CHR state (e.g., by additional occurrence or an increase in frequency of COGDIS symptoms) might index an ongoing imbalance of excessive synaptogenesis/pruning in critical networks, and ultimately the emergence of diagnostically relevant psychotic symptoms. This is supported by a recent analysis of two general population samples spanning the age of 8–40 years (66). Age seemed to affect the 14 perceptive and cognitive BSs included in COPER and COGDIS differently, indicating an age threshold of perceptive BS in late adolescents, around age 18, and of cognitive BSs in young adulthood, in the early twenties – with higher prevalence but reduced association to functional deficits and presence of mental disorder in the below-threshold groups. Thereby, differential age effects seem to follow normal back-to-front brain maturation processes, during which BSs might occur as temporary, in most cases infrequently occurring non-pathological disturbances. Their persistence or onset after conclusion of main brain maturation processes, however, might signify aberrant brain processes. Furthermore, an alternative or complementary explanation of this age-related pattern might be given against the background of decreasing brain plasticity after myelination and pruning processes reach maturity in the early 20s (67): BSs developing in childhood and adolescence, or rather their underlying neurobiological aberrations, might be much better compensated for by the still developing brain and thus, despite the larger number of affected youths, might only be reported by them as infrequent, momentary phenomena. These assumptions might be examined in future studies (i) by cross-sectionally comparing brain development in adolescents reporting BSs with and without clinical significance, (ii) by comparing subjects with an onset of BSs before and after age 18, and (iii) by comparing non-converters and converters to psychosis with regard to their onset and course of BSs.

In addition, if BSs reflect brain processes related to psychosis, then manifestation of BSs should closely be linked to genetic risk. Indeed, studies on first-degree relatives (7, 68–70) and schizotypal samples (71–73) indicated increased rates of BSs compared to HCs and non-schizophrenia-spectrum patients, respectively. In first-degree relatives, this involved more specific cognitive, perceptive and stress-tolerance-related BSs in particular (68). A recent genome-wide association study (74) identified 108 genetic variants associated with biological pathways central to the pathophysiology of schizophrenia. Thus, another route of future studies could be to explore links between certain BSs and possibly related risk-variants, e.g., between certain cognitive BSs and SNPs involved in cognition related neurotransmission.

Additional insights into the neurobiological basis of BSs might also be gained by using pharmacological perturbations in healthy samples. Preliminary evidence indicates that ketamine as well as THC may be associated with the expression of BSs (22, 23). Further studies in healthy populations using a range of pharmacological models which target specific cannabinoid, glutamatergic, dopaminergic, and GABAergic systems could provide important information on the contribution of dysfunctions in neurotransmitter systems and manifestation of BSs.

Finally, studying CHR patients at different stages may reveal the neurobiological correlates of BSs and evolution of schizophrenia. Theoretical and empirical evidence suggests that BSs may constitute the earliest signposts, preceding the development of UHR and psychotic symptoms. Recent studies point toward anatomical and electrophysiological differences between BSs and UHR samples; but these findings require replication and extension with functional imaging approaches. Longitudinal investigations of individuals identified on the basis of BSs alone could provide crucial information on their neurobiological correlates and potential progressive pathophysiological processes that might lead eventually to psychosis.

CONCLUSION

In conclusion, despite the fact that BSs were in their original (and pioneering) formulation considered to be a direct manifestation of brain abnormalities in patients with schizophrenia, the nature of such abnormalities appear subtle and heterogeneous, requiring sophisticated methods of analyses to be detected. Our review suggests that the CHR paradigm may constitute a fruitful paradigm to investigate the relationship between phenomenologically grounded perceptual and cognitive alterations and underlying abnormalities in the functionality of anatomical and functional brain networks. These insights may not only be useful for an improved general understanding of BSs but may ultimately give critical insights into the development of psychosis, which could be crucial for early diagnosis and intervention. Furthermore, as BSs are not only present in the initial prodromal phase, but throughout the course of the illness, they may also enable new insights into the neurobiological determinants of unfavorable outcomes including functional deterioration.

AUTHOR CONTRIBUTIONS

FS-L and PU wrote the outline of the article. All authors managed the literature searches to draft their respective chapters. FS-L drafted the introduction and parts 1 and 3 of the Supplementary Material; CM drafted the chapter on Neurocognition and BSs; AT and JK drafted the chapter on Neurochemistry and BSs; PU drafted the chapter on

Electrophysiology and BSs and the discussion; MD drafted the chapter on Neuroimaging and BSs; AR drafted part 2 of the Supplementary Material. All authors contributed to and have approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org//article/10.3389/fpsyt.2016.00009

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Conflict of Interest Statement: Stephan Ruhrmann served as a consultant for Boehringer Ingelheim, received Speaker's honoraria from Otsuka and Johnson & Johnson, and travel support from Servier. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 08 April 2016
doi: 10.3389/fpsyt.2016.00052

Identifying Individuals at High Risk of Psychosis: Predictive Utility of Support Vector Machine using Structural and Functional MRI Data

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The identification of individuals at high risk of developing psychosis is entirely based on clinical assessment, associated with limited predictive potential. There is, therefore, increasing interest in the development of biological markers that could be used in clinical practice for this purpose. We studied 25 individuals with an at-risk mental state for psychosis and 25 healthy controls using structural MRI, and functional MRI in conjunction with a verbal memory task. Data were analyzed using a standard univariate analysis, and with support vector machine (SVM), a multivariate pattern recognition technique that enables statistical inferences to be made at the level of the individual, yielding results with high translational potential. The application of SVM to structural MRI data permitted the identification of individuals at high risk of psychosis with a sensitivity of 68% and a specificity of 76%, resulting in an accuracy of 72% ($p < 0.001$). Univariate volumetric between-group differences did not reach statistical significance. By contrast, the univariate fMRI analysis identified between-group differences ($p < 0.05$ corrected), while the application of SVM to the same data did not. Since SVM is well suited at identifying the *pattern of abnormality* that distinguishes two groups, whereas univariate methods are more likely to identify regions that *individually* are most different between two groups, our results suggest the presence of focal functional abnormalities in the context of a diffuse pattern of structural abnormalities in individuals at high clinical risk of psychosis.

Keywords: psychosis, risk, support vector machine, MRI and fMRI, at-risk mental state, schizophrenia, verbal learning, memory

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Kerstin Bendfeldt, University of Basel, Switzerland
Aaron Leonard Mishara, The Chicago School of Professional Psychology, USA

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *21 January 2016*
Accepted: *23 March 2016*
Published: *08 April 2016*

Citation:
Valli I, Marquand AF, Mechelli A, Raffin M, Allen P, Seal ML and McGuire P (2016) Identifying Individuals at High Risk of Psychosis: Predictive Utility of Support Vector Machine using Structural and Functional MRI Data. Front. Psychiatry 7:52. doi: 10.3389/fpsyt.2016.00052

INTRODUCTION

At present, it is possible to identify individuals at a greatly increased risk of developing psychosis on the basis of clinical features that may include attenuated psychotic symptoms (1), schizotypal personality traits (2), a positive family history of psychosis, and a marked decline in overall function (3). Individuals presenting with these features are defined as having an at-risk mental state (ARMS) (1), which is associated with a risk of subsequent transition to psychosis of 18% after 6 months

of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years (4). However, there is increasing evidence that psychotic experiences are quite common among adolescents and young adults in the general population (5), and the particular clinical criteria that should be used are still being debated (6). This has led to interest in neurobiological markers of psychosis risk.

Structural magnetic resonance imaging (sMRI) studies have provided robust evidence for structural brain abnormalities in high-risk populations, with the most pronounced gray matter (GM) differences relative to healthy controls observed in the prefrontal, cingulate, lateral, and medial temporal cortices (7, 8). These regions are critical for episodic memory performance, which is reported to be impaired in the ARMS (9). Verbal episodic memory deficits were found to be associated with reductions in GM volume (GMV), particularly in the medial temporal cortex, not only in the ARMS (10) but also in non-psychotic relatives of individuals with schizophrenia (11). A small number of studies have investigated the functional correlates of episodic memory dysfunction in the ARMS (9), including work from our group on a sample partially overlapping with the present one, which identified activation abnormalities in brain regions, including prefrontal and medial temporal cortices (12, 13). These studies were conducted with a univariate analytical approach. Multivariate analysis methods, such as support vector machine (SVM)(14, 15), offer the advantage of enabling statistical inferences to be made at the level of the individual and, therefore, yield results with high translational potential in clinical practice. In particular, SVM is a technique for classifying individual observations into distinct groups or classes, based on the detection of regularities in high-dimensional data (16). The use of multivariate analysis approaches has previously demonstrated the potential of structural MRI data for the discrimination of patients with schizophrenia from healthy controls, with 81 and 86% diagnostic accuracies observed for patients with chronic schizophrenia (15) and first-episode patients (17), respectively. Considerable interest lays in the potential of these approaches to identify individuals at risk of the disorder and to identify which individuals will develop psychosis among those that show a vulnerability to it. A recent study addressing this issue found that the structural neuroanatomy of high-risk individuals provided information that permitted their distinction from controls with an 86% accuracy, irrespective of clinical outcome, and further indicated that structural abnormalities were most pronounced in the individuals who went on to develop psychosis (18). The first study using a pattern classification approach for the analysis of neurocognitive parameters in high-risk individuals obtained a 94.2% accuracy in distinguishing vulnerable individuals from healthy controls, with discriminatory patterns involving mainly verbal learning and memory domains (19). A further analysis aiming to discriminate individuals that subsequently developed psychosis from the rest of the participants resulted in 90.8% accuracy, with transition to psychosis mainly predicted by executive and verbal learning impairments (19). However to date no study has investigated the potential of the functional correlates of verbal learning for identifying individuals at high-risk for psychosis using a multivariate approach. The aim of the present investigation was, therefore, to use a standard univariate analysis and a SVM classifier to examine structural imaging data and the functional correlates of a verbal memory task. We hypothesized that SVM applied to structural and functional imaging data, respectively, would permit the identification of individuals with an ARMS with statistically significant accuracies.

MATERIALS AND METHODS

The protocol of the study was in compliance with the Code of Ethics of the World Medical Association, it was approved by the research ethics committee of the Institute of Psychiatry, King's College London, and all participants gave written informed consent to participate after a complete description of the study.

Participants

Twenty-five individuals meeting criteria for an ARMS were recruited from Outreach and Support in South London (20), a clinical service for people at risk of developing psychosis. The diagnosis was based on the PACE criteria (21), as assessed by two expert clinicians using the Comprehensive Assessment for At-Risk Mental States (CAARMS) (22) and confirmed at a consensus clinical meeting. All subjects were antipsychotic naïve at the time of scanning, and six were receiving antidepressant medication. Twenty-five control subjects were recruited over the same period from the same sociodemographic area. Subjects were aged 18–30 years and were all native speakers of English. Participants were excluded if their IQ was below 70, if they had a history of a neurological disorder, a history of severe head injury, or if they met DSM-IV criteria for an alcohol or drug dependence disorder. An additional exclusion criterion for control subjects was a family history of psychosis. The study includes all participants reported in a previous manuscript (9) that investigated a subsample of the current ARMS and control groups.

All participants, with the exception of one for each group, were right handed as evaluated using the Lateral Preferences Inventory (23).

Clinical Measures

Current symptoms were assessed in all participants at the time of scanning using the Positive and Negative Syndrome Scale (PANSS) (24). Premorbid IQ was estimated with the Wide Range Achievement Test-Revised (WRAT-R) (25).

Statistical Analyses

Statistical analyses were conducted using SPSS version 16.0 (SPSS inc. Chicago, IL, USA). Student's *t*-test was used to compare ARMS and control participants in terms of demographic and clinical variables.

Image Acquisition

Images were acquired using a 1.5-T GE NV/I Signa LX Horyzon system (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, King's College London.

Structural Images

T1-weighted inversion recovery spoiled gradient structural images were acquired with the following acquisition

parameters: TE = 5200 ms, TR = 15900 ms, flip angle = 20°, field of view = 220 mm × 176 mm, slice thickness = 1.5 mm, number of slices = 124, image matrix = 256 × 256 × 124.

Functional Images

T2-weighted images were acquired using gradient-echo echoplanar magnetic resonance imaging (EPI) during the Encoding and the Recognition condition of an episodic verbal memory paradigm previously described (12). The data reported here refer to the encoding condition, in which 160 words were visually presented in blocks of 10 words each, back projected with an LCD projector on to a screen viewed through a prism positioned over the head coil. Participants were asked to read words aloud and try to remember them. Stimuli were presented with stimulus onset asynchrony of 4 s. Between each encoding block, there was a word repetition condition in which subjects were required to repeatedly view and say the word "wait" in blocks of four presentations each. Participants were aware that the encoding task would be followed by a test of recognition of the presented material. During the encoding condition, 228 image volumes were acquired in a single functional run using a compressed acquisition sequence (TR = 4000 ms, silent period 2500 ms) to allow verbal articulation of the stimuli in the absence of acoustic scanner noise and to minimize motion artifacts related to overt articulation. Images were acquired in 16 non-contiguous axial planes parallel to the intercommissural plane with the following parameters: TE = 40 ms, slice thickness = 7 mm, slice skip = 0.7 mm, in plane resolution 3 mm × 3 mm.

Univariate Analysis

Structural Imaging Analysis

Group-related differences in GMV were analyzed using voxel-based morphometry (VBM), implemented in SPM8 software[1] running under Matlab 7.4 (MathWorks, Natick, MA, USA). Prior to the VBM analysis T1-weighted volumetric images were preprocessed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) (26) SPM8 toolbox, aimed at maximizing analysis accuracy and sensitivity through the creation of a sample-specific template that is used for the segmentation of each individual image (27). After the image origin was set manually to the anterior commissure, T1-weighted images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF). GM segments were iteratively registered by non-linear warping to a template generated using DARTEL to obtain a high-dimensional normalization (26). A homogeneity check across the sample was followed by smoothing with an 8 mm full width at half maximum (FWHM) Gaussian kernel. The normalization protocol included a "modulatory step" in order to preserve information about the absolute GM values (28). After preprocessing, normalized modulated smoothed data were used for the statistical analysis. This was performed using SPM8 to compare GM images from ARMS participants and controls with a two-sample *t*-test. Age, gender, and medication were modeled in the analysis to reduce the potential impact of these variables on the findings. In order to identify specific changes not confounded by global volumetric differences, the proportional scaling option was used. Statistical inferences for the standard univariate analysis were made whole brain voxel-wise at $p < 0.05$ family wise error (FWE).

Functional Imaging Analysis

Functional images were realigned to the first volume in the series to correct for movement during acquisition, transformed into a standard space (SPM EPI template) and smoothed using a 6-mm isotropic Gaussian filter using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK, see text footnote 1) running in matlab 7.4 (MathWorks, Natick, MA, USA). A standard random effects statistical analysis of regional responses was performed to identify regional activations in each subject independently. To remove low-frequency drifts, the data were high-pass filtered using a set of discrete cosine basis functions with a cut off period of 128 s.

Each stimulus was modeled independently by convolving the onset times with the hemodynamic response function (HRF). First, the parameter estimates for encoding and repetition were calculated using the general linear model in each individual subject. Second a group analysis was performed using a 2 × 2 factorial model of variance (ANOVA), with group (ARMS, controls) and condition (encoding, repetition) as factors. Age, gender, and medication were modeled as covariates to minimize the impact of these potentially confounding variables on the results. The whole brain voxel-wise threshold was set at $p < 0.05$ FWE corrected.

Regression coefficients ("beta values"), which provide information about the fit of the regressor to the data at each voxel, were obtained for each subject, masked to include only intracerebral tissue, then used for the multivariate analysis of the Encoding condition.

Multivariate Analysis

A linear SVM was used to classify ARMS participants and controls on the basis of their brain structure. A separate analysis was performed on the basis of their brain activation during the Encoding phase of a verbal episodic memory task. The SVM classifier was implemented using the PROBID software[2] (Institute of Psychiatry, London, UK) running in matlab 7.4. (MatWorks, Natick, MA, USA).

Classification and Support Vector Machine

Support vector machine is a supervised multivariate classification method where "supervised" refers to a training step in which the algorithm learns the differences between pre-specified groups to be classified (29). SVM treats each image as a point in a high-dimensional space, where the number of dimensions equals the number of intracerebral voxels. Participants were allocated to one of two classes (ARMS or controls) and a linear classification function was learnt from the imaging data in order to discriminate between the two groups. To linearly classify the data, a decision boundary or hyperplane (a generalization of

[1] http://www.fil.ion.ucl.ac.uk/spm

[2] www.brainmap.co.uk/probid.htm

a plane of $n - 1$ dimensions that splits an n-dimensional space) must be defined in order to separate the data based on class membership. However, for a linearly separable problem, there are infinitely many hyperlanes that correctly classify the data. The SVM algorithm (30) finds the optimal one in the sense that it is characterized by the largest margin between classes. The margin is defined as the distance of the closest training data-points to the hyperplane. These points are the most difficult to classify and are called support vectors. The hyperplane is defined by a weight vector, which is a linear combination of the support vectors and specifies both a direction and an offset that together define the maximum margin classifier. The SVM regularization parameter (conventionally denoted "C") was fixed to its default value (1), following common practice in neuroimaging studies.

Discrimination Maps

The weight vector is normal to the hyperplane and can be conceptualized as a spatial representation of the decision boundary. It has the same dimension as the training data (in this case voxel space) and can, therefore, provide a map of the most discriminatory regions (discrimination map). If the two groups are attributed labels of +1 and −1, higher positive values indicate regions making a positive contribution toward identifying the first group relative to the second and vice versa, indicating which regions are most important for defining class membership for the first and the second group, respectively [for a description see Ref. (31)]. In the present study, positive values were associated with the ARMS group and coded in red/yellow color scale, while the control group was associated with a negative weight and coded in blue/cyan color scale. The multivariate nature of the classifier provides a spatial pattern of regions that discriminate between the two groups.

Classifier Performance

The performance of the classifier was assessed using a leave-one-out cross-validation procedure (16). This approach consists of training the classifier with all participants except from one pair and subsequently testing the group membership assigned to the excluded subjects. This test was repeated 25 times, each time excluding a different pair of participants, one from the ARMS group and one from the control group. This procedure permitted the measurement of the accuracy of the classifier, defined as the proportion of correctly classified participants. It also permitted the quantification of the sensitivity and specificity of the classifier, defined as follows:

- Sensitivity = TP/(TP+FN)
- Specificity = TN/(TN+FP)

TP refers to true positives, which is the number of individuals from the ARMS group correctly classified. TN, or true negatives, is the number of individuals from the control group correctly classified. FP, or false positives, refers to the number of control participants misclassified as belonging to the ARMS group, while FN, or false negatives, is the number of ARMS participants misclassified as belonging to the control group.

Permutation Testing

The significance of the SVM classification was assessed at whole-brain level using a non-parametric permutation test. This evaluates the probability of obtaining by chance sensitivity and specificity values higher than those obtained during the leave-one-out cross-validation procedure. This method randomly assigns participants to one of the classes before training the SVM. In the present study, 1000 permutations were conducted and the null hypothesis of the observed classification being observed by chance was rejected for $p = 0.05$. The discrimination maps show the most important regions contributing to an overall accuracy significant at the $p < 0.05$ level.

RESULTS

Demographic and Clinical Variables

The two groups were matched in terms of age and estimated premorbid IQ. There was a larger proportion of male participants in the ARMS group (72%) than in the control group (56%), though not statistically significant.

As expected, the two groups differed in terms of symptom severity as assessed using the PANSS total score and each of the subscales (**Table 1**).

Imaging Results

Univariate Structural Analysis

When VBM was used, volumetric between-group differences were observed only at uncorrected level but none reached a trend for significance with correction for multiple comparisons ($p < 0.05$, FWE corrected).

Univariate Functional Analysis

During the encoding condition, controls showed greater activation than ARMS subjects in the left middle frontal and precentral gyri, supramarginal gyrus, and insula as well as the right medial frontal gyrus (**Table 2**, **Figure 1**).

TABLE 1 | Demographic and clinical variables by group.

	Group		Group comparison
	ARMS (*N* = 25)	**Controls (*N* = 25)**	
Age (years)	23.84 (5.52)	25.12 (3.21)	$t = -1.003$, $p = 0.322$
N, Male/Female	18/7	14/11	$\chi^2 = 1.389$, df = 1, $p = 0.239$
Premorbid IQ	101.48 (13.20)	104.12 (8.80)	$t = -0.832$, $p = 0.410$
PANSS	46.40 (9.51)	30.44 (0.96)	$t = 8.35$, $p < 0.001$
PANSS positive	12.48 (3.19)	7.2 (0.50)	$t = 8.18$, $p < 0.001$
PANSS negative	10.16 (4.06)	7.00 (0.00)	$t = 3.89$, $p < 0.001$
PANSS general	23.80 (5.45)	16.24 (0.66)	$t = 6.88$, $p < 0.001$

Data reflect mean (and SD). Df (degrees of freedom) = 48; N = number; PANSS, Positive and Negative Syndrome Scale.

TABLE 2 | Main effect of Encoding.

Brain region	x	y	z	z-score
L insula	−32	−24	4	5.46
L precentral gyrus	−32	6	42	5.34
R medial frontal gyrus	22	44	20	5.11
L middle frontal gyrus	−52	34	20	4.74
L supramarginal gyrus	−46	−52	24	4.56

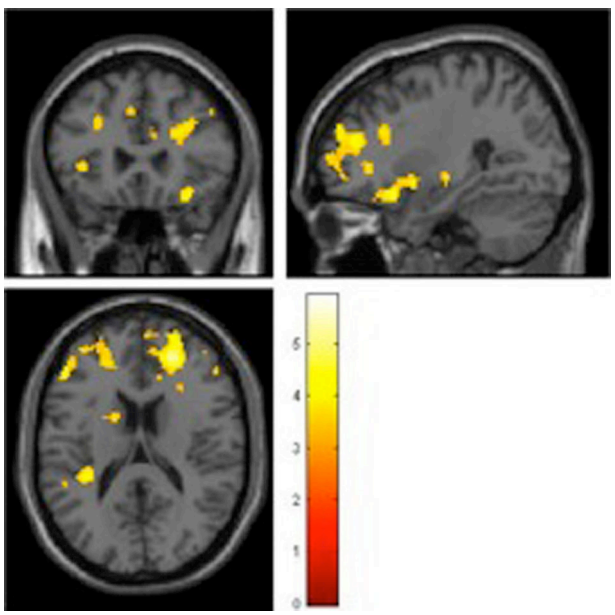

FIGURE 1 | Main effect of Encoding (FWE corrected).

Multivariate Structural Analysis

The structural neuroanatomy of individuals at risk of psychosis permitted their discrimination from healthy controls at a statistically significant level ($p < 0.001$) with 68% sensitivity and 76% specificity, resulting in 72% accuracy.

The neuroanatomical pattern distinctive of the ARMS group (i.e., having high magnitude positive weights) showed high weights bilaterally in the hippocampus, parahippocampal gyrus, putamen, superior and middle frontal gyri, middle temporal gyrus, fusiform gyrus, and inferior parietal lobule. In addition, lateralized findings distinctive of ARMS group membership included the left inferior temporal gyrus, right superior temporal gyrus, left precuneus, and left cerebellum (**Figure 2**).

The pattern distinctive of the control group (i.e., having high magnitude negative weights) showed high weights bilaterally in the medial and inferior frontal gyri, the inferior and middle temporal gyri, the insula, the cuneus, the cerebellum, anterior, and posterior cingulate. Lateralized findings distinctive of control group membership included the left superior and middle frontal gyri, the left middle occipital gyrus and right precuneus (**Figure 2**).

Multivariate Functional Analysis

Based on the functional imaging data, no significant discrimination of ARMS subjects relative to controls was obtained, with between-group discrimination no greater than chance ($p = 0.34$), sensitivity of 48%, specificity of 60%, and overall accuracy of 54% when the leave-one-out cross-validation procedure was employed.

DISCUSSION

Identification of psychosis prone individuals still uses a method available 100 years ago – a clinical interview. In the rest of medicine, investigations often involve the use of biological tests, which can help to identify conditions of risk, and allow earlier detection of the disorder. In the absence of diagnostic biomarkers for psychosis, methods that permit the distinction of vulnerable individuals from healthy controls have important implications for the early detection and diagnosis of the disorder.

Structural and functional MRI data were used to assess their potential to reliably distinguish control and ARMS individuals using multivariate analysis techniques.

The results indicated that the multivariate approach enabled the identification of structural differences that distinguished the two groups. By contrast, the univariate analysis of the functional MRI data identified significant group differences, while the SVM method did not. In the present study, the sample size may have limited the power to identify group differences, but their detection with one analytical method rather than the other may alternatively reflect a different distribution of structural and functional abnormalities. Univariate analytical approaches consider each voxel independently and are well suited to detecting effects that are localized and robust; by contrast, multivariate methods take into account between-voxel correlations and are ideal for detecting subtle and spatially distributed patterns of abnormality (32). If SVM is well suited at finding the *set of areas* that jointly distinguish two groups, whereas univariate methods are more likely to identify regions that *individually* are most different between two groups, our results suggest the presence of focal functional abnormalities in the context of a diffuse pattern of structural abnormalities.

Based on previous SVM findings, both in schizophrenia (15, 17) and in the ARMS (32), it was predicted that structural MRI data would allow a robust between-group discrimination. In the present sample, using a leave-one-out procedure, the whole-brain structural correlates of the ARMS identified individuals belonging to this group relative to healthy controls with 72% accuracy. This is lower relative to accuracy levels previously reported for schizophrenia (15, 17), and in a previous MRI study in the ARMS (18). Nevertheless, the classification was highly significant under permutation ($p < 0.001$). The results, therefore, replicate previous findings, albeit with a relatively lower accuracy, and suggest that the high risk of psychosis seen in people with an ARMS is associated with significant alterations in brain anatomy.

Some of the regions identified as most important for discriminating between ARMS and controls feature within circuits connecting the medial temporal region to the lateral temporal and prefrontal cortices (33), networks that normally play an

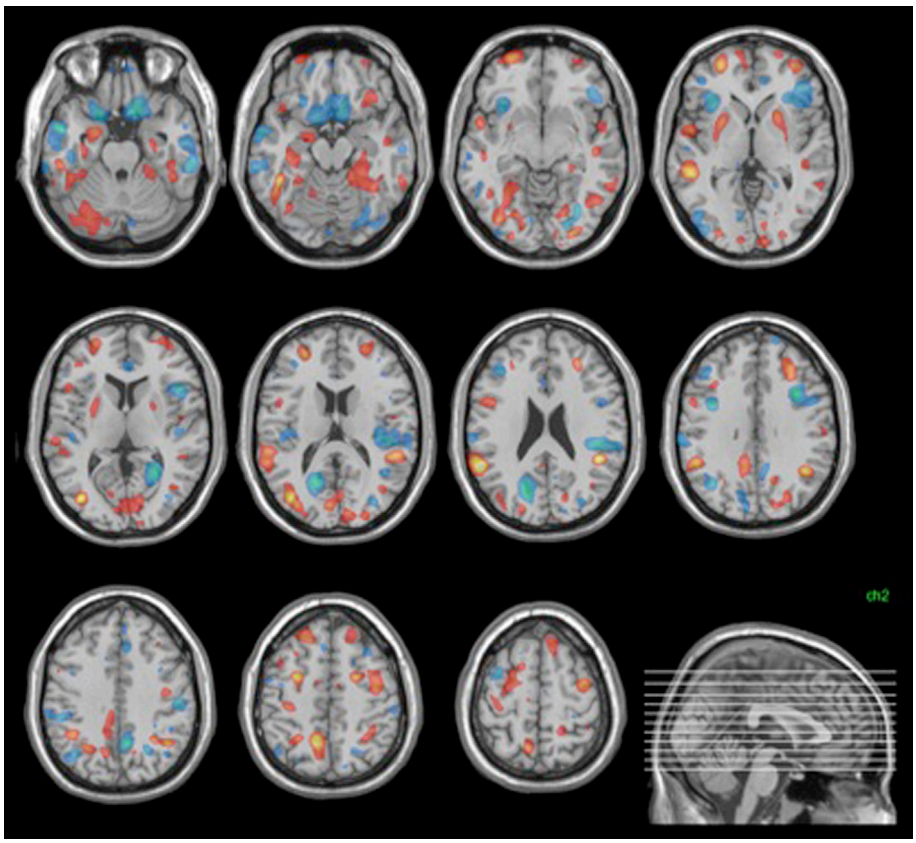

FIGURE 2 | **Structural discrimination map**. Areas shown in red were those most distinctive of ARMS group membership. Those in blue were most distinctive of control group membership. Images were thresholded to show the top 30% of voxel weight vector values (positive and negative).

important role in episodic memory (34). However, the SVM analysis of the functional MRI data acquired during an episodic memory task failed to reliably distinguish the ARMS participants from healthy controls. These data, thus, suggest that activation during the encoding phase of an episodic memory task may not have potential for the identification of group membership in this context. Nevertheless, we cannot exclude the possibility that a significant difference might have emerged had the sample size been larger. A previous investigation, which used fMRI in conjunction with an *n*-back working memory task to discriminate between ARMS individuals and healthy controls (35), reported a statistically significant accuracy of 76.2%. However, we note that this investigation was also carried out in a small sample of 19 ARMS and 19 healthy controls. In order to address the apparent inconsistency between the results of this previous investigation and those of our study, replication with a larger sample size and multiple memory tasks (e.g., working vs. episodic memory) would be required, especially considering the clinical heterogeneity of the population under investigation.

When structural imaging data are considered using machine learning methods, the findings cannot be interpreted simply in terms of greater or lower GMV in one group relative to the other. The set of areas identified in each group represent the brain regions that are the most important for predicting membership of each group. Regions in the predictive pattern can be assigned high weight vector scores either because of a large difference in GMV, or because the region adds predictive value by virtue of its correlation with other brain regions [e.g., to cancel out noise (36)]. In previous studies of schizophrenia, the predictive pattern from the multivariate analysis mostly implicated regions similar to those where volumetric reductions had been identified using univariate analyses (15, 37), with differences mainly in frontal, temporal, parietal, and cingulate cortices, the medial temporal lobe and the thalamus (38, 39). Similarly, the recent application of machine learning techniques to MRI data in the ARMS characterized the high-risk population by a distributed pattern comprising frontal, temporal, limbic, and cerebellar regions (18, 32). The present SVM results derived from structural data were consistent with those from previous studies, with the classification pattern containing clusters in the prefrontal and temporal cortices, and a large bilateral cluster, including the hippocampus and parahippocampal gyrus. These are areas where volumetric abnormalities have been indentified using univariate analyses in ARMS and genetic high-risk individuals relative to controls (40–42). While data from univariate MRI studies indicate that vulnerability to psychosis is associated with GM abnormalities regardless of clinical outcome (7, 41), there is also evidence that later transition to psychosis is associated with more marked abnormalities at baseline (7, 41)

and with progressive volumetric reductions between baseline and the onset of psychosis (40, 43). These findings are not mutually exclusive: it is likely that the former are correlates of increased risk (independent of subsequent clinical outcome), while the latter are specific correlates of later illness. The first studies to address the issue of abnormalities specific to those subjects who will develop psychosis have provided promising results, with machine learning classifiers appearing able to distinguish subjects that would subsequently develop psychosis from those who would not, based on structural abnormalities present before psychosis onset (18). However, the clinical follow-up of the ARMS participants is still ongoing and no direct comparison was performed based on outcome; therefore, no inferences can be made relative to abnormalities specific to later transition to psychosis.

The present study had further limitations. First, the sample sizes were relatively small, which may have limited its power to detect true group differences. As discussed above, this means that the negative findings in the structural and functional analyses must be interpreted with caution, and future studies using larger samples are needed to address this issue as well as that of specificity relative to other psychiatric disorders. There was a higher proportion of male participants in the ARMS than that of the control group. The gender difference did not reach significance; however, it represents a possible confounder because of the sexual dimorphism of brain structure and development (44, 45) and the gender differences reported in brain morphology in schizophrenia (46). Finally, even though all the ARMS participants were antipsychotic naïve, six of them had been exposed to antidepressant medication. It is, therefore, not possible to rule out whether this variable may have contributed to the differences observed (47).

In conclusion, we found that a multivariate analysis of neuroanatomical images enabled the identification of individuals at high risk of psychosis with statistically significant accuracy. By contrast, the functional correlates of episodic memory did not show classification potential in this clinical population. Mass-univariate analyses are optimal for identifying focal group differences, and are more sensitive than multivariate methods if the effects are localized to particular brain regions. Multivariate methods, on the other hand, are sensitive to spatially distributed patterns of activity, and are more sensitive if the differential effects are distributed across widespread brain regions. The two analyses are, therefore, complementary and address different questions when used in combination. These results expand the current understanding of structural and functional brain abnormalities in individuals at high risk of psychosis. Future work could examine possible strategies to improve the diagnostic and prognostic classification of this clinical population, for example, through the integration of multiple modalities within a multivariate machine learning framework.

AUTHOR CONTRIBUTIONS

All persons designated as authors have participated in the work and have reviewed the manuscript.

FUNDING

This work was supported by a Medical Research Council Clinical Training Fellowship awarded to IV (grant No G0601437) and a National Alliance for Research on Schizophrenia and Depression Young Investigator Award awarded to PA. AFM gratefully acknowledges support from King's College London Centre of Excellence in Medical Engineering, funded by the Wellcome Trust and the Engineering and Physical Sciences Research Council under Grant number WT088641/Z/09/Z and also the Netherlands Organisation for Scientific Research under the Language in Interaction project.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer KB and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 31 March 2016
doi: 10.3389/fpsyt.2016.00050

Detecting Neuroimaging Biomarkers for Psychiatric Disorders: Sample Size Matters

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In a recent review, it was suggested that much larger cohorts are needed to prove the diagnostic value of neuroimaging biomarkers in psychiatry. While *within* a sample, an increase of diagnostic accuracy of schizophrenia (SZ) with number of subjects (*N*) has been shown, the relationship between *N* and accuracy is completely different *between* studies. Using data from a recent meta-analysis of machine learning (ML) in imaging SZ, we found that while low-*N* studies can reach 90% and higher accuracy, above $N/2 = 50$ the maximum accuracy achieved steadily drops to below 70% for $N/2 > 150$. We investigate the role *N* plays in the wide variability in accuracy results in SZ studies (63–97%). We hypothesize that the underlying cause of the decrease in accuracy with increasing *N* is sample heterogeneity. While smaller studies more easily include a homogeneous group of subjects (strict inclusion criteria are easily met; subjects live close to study site), larger studies inevitably need to relax the criteria/recruit from large geographic areas. A SZ prediction model based on a heterogeneous group of patients with presumably a heterogeneous pattern of structural or functional brain changes will not be able to capture the whole variety of changes, thus being limited to patterns shared by most patients. In addition to heterogeneity (sample size), we investigate other factors influencing accuracy and introduce a ML effect size. We derive a simple model of how the different factors, such as sample heterogeneity and study setup determine this ML effect size, and explain the variation in prediction accuracies found from the literature, both in cross-validation and independent sample testing. From this, we argue that smaller-*N* studies may reach high prediction accuracy at the cost of lower generalizability to other samples. Higher-*N* studies, on the other hand, will have more generalization power, but at the cost of lower accuracy. In conclusion, when comparing results from different ML studies, the sample sizes should be taken into account. To assess the generalizability of the models, validation (by direct application) of the prediction models should be tested in independent samples. The prediction of more complex measures such as outcome, which are expected to have an underlying pattern of more subtle brain abnormalities (lower effect size), will require large samples.

Keywords: machine learning, effect size, heterogeneity, classification and prediction, neuroimaging, schizophrenia

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Joseph Kambeitz, University of Munich, Germany
Paolo Brambilla, University of Milan, Italy

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *04 December 2015*
Accepted: *16 March 2016*
Published: *31 March 2016*

Citation:
Schnack HG and Kahn RS (2016) Detecting Neuroimaging Biomarkers for Psychiatric Disorders: Sample Size Matters. Front. Psychiatry 7:50. doi: 10.3389/fpsyt.2016.00050

INTRODUCTION

Since the recent development and application of machine learning (ML) techniques in neuroimaging data for classification and prediction of psychiatric disorders, dozens of studies have been published on the use of (structural and functional) MRI scans for, e.g., classification of schizophrenia (SZ) [for a recent overview, see Ref. (1)], autism (2), ADHD (3), the separation of bipolar disorder from SZ (4), prediction of outcome/illness course in SZ and related psychotic disorders (5, 6), transition to psychosis (7), and distinguishing prodromal from first-episode psychosis (8) at the level of the individual. The published values of the prediction accuracy, the standard measure of the performance, of the binary classification models, range from a little above 50% (rolling the dice) up to (and including!) 100% (1, 9, 10). The sample sizes used in these studies vary between 15 and 198 per diagnostic group. Although, such as in group-level statistics, it has been shown that sample size matters and that classification accuracy in small samples show large variation (11), a substantial number of studies with low *N* has been published. While this is usually justified for pilot studies, proof of principle studies, and studies on "difficult" samples (difficult inclusion or using challenging imaging techniques), they do not support conclusions about the potential of the technique to be used in a clinical setting. It has recently been suggested that ML studies with larger samples should be conducted in order to be of diagnostic value (12) and we think the time has come to make the step toward a next "generation" of ML studies, using large samples and/or independent validation samples and (re)use (smaller) studies. In this work, we will try to interpret the variations in performance seen in published ML neuroimaging studies. To do this, we will introduce the ML effect size as a measure of the predictive power of a model and develop a theoretical model to quantify the relationship between sample heterogeneity and prediction accuracy. We will conclude with a number of recommendations for psychiatric neuroimaging ML studies in the future.

Machine Learning Studies in Psychiatric Imaging: Schizophrenia

We base our approach on the observations from published sMRI-ML studies on SZ summarized in **Figure 1**. The figure clearly illustrates two phenomena: (1) published ML models from smaller samples yield higher classification accuracies and the observed accuracies appear to lie on (and below) a line that divides the diagram in two and (2) replications in independent validation samples yield lower accuracies, also decreasing with (training) sample size. These effects may be explained by (at least) two reasons: sample homogeneity and publication bias. Poorer performing models in small samples may remain unpublished, while this variation in accuracy may be due to chance (11) as well as better performance in homogeneous (small) samples. The lower accuracy in the larger samples can be ascribed to increased within-sample heterogeneity; these models may better capture the "complete picture" of SZ patterns. These models generalize better to other samples drawn from different populations at the cost of a lower accuracy. From all applications of ML in neuroimaging, those in psychiatry seem to be affected most severely by the effects of small samples, given the heterogeneous nature of the disorders, both in appearance and in underlying brain features (13). In the following, we will setup a simple theoretical framework to describe the different factors that affect a prediction model's performance. The resulting formulas can be used to (1) quantitatively relate the observed fall in classification accuracy for increasing sample size to *within-sample* heterogeneity and (2) determine the *between-sample* heterogeneity, i.e., the non-overlap in sample characteristics from the accuracy difference in a test/retest study. These tools can also be applied to (*post hoc*) multicenter ML studies to unravel the heterogeneity of the brain biomarker structure related to psychiatric disorders.

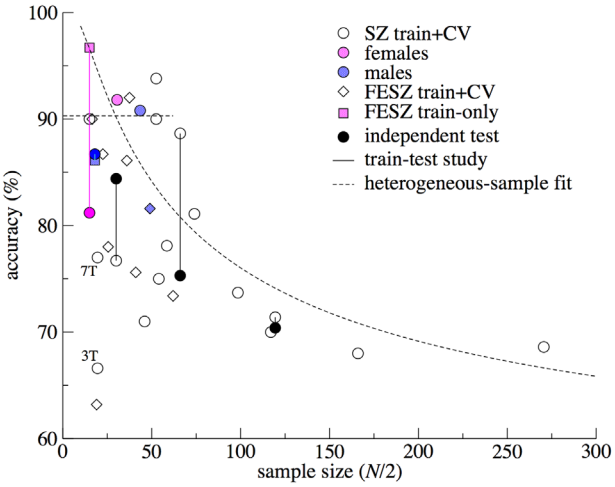

FIGURE 1 | Prediction accuracy versus sample size for the schizophrenia machine learning studies using structural MRI. Data are taken from the reviews by Zarogianni et al. (9) and Kambeitz et al. (1) and some (recent) studies (4, 14–18). Sample size *N*/2 was calculated as the mean of the patient and control sample sizes. Different symbols mark cross-validation accuracy from studies on chronic/mixed patients (circles) and first-episode patients (diamonds). Soft colors were used to indicate studies that included only females (pink) or males (blue). Train accuracy without cross-validation is marked by squares. Lines connect train–test studies, where the accuracy in the independent test sample is marked with solidly filled symbols. "3T" and "7T" mark the study by Iwabuchi (19), using the same subjects scanned at different field strengths. Curved dashed line: heterogeneous-sample theory. Horizontal dashed line: stretched range of homogeneous samples.

METHODS AND RESULTS

Accuracy of Machine Learning Models: Effect Size

Figure 2A summarizes the process of applying ML to imaging data and the resulting classification performance. Every subject is represented by a so-called feature vector x that contains the features, or measures, that will be used to separate the two groups. These features can consist of any set of (neuroimaging) measures, for instance, a set of atlas-based regional brain volumes (low-dimensional feature space), or voxelwise gray matter densities

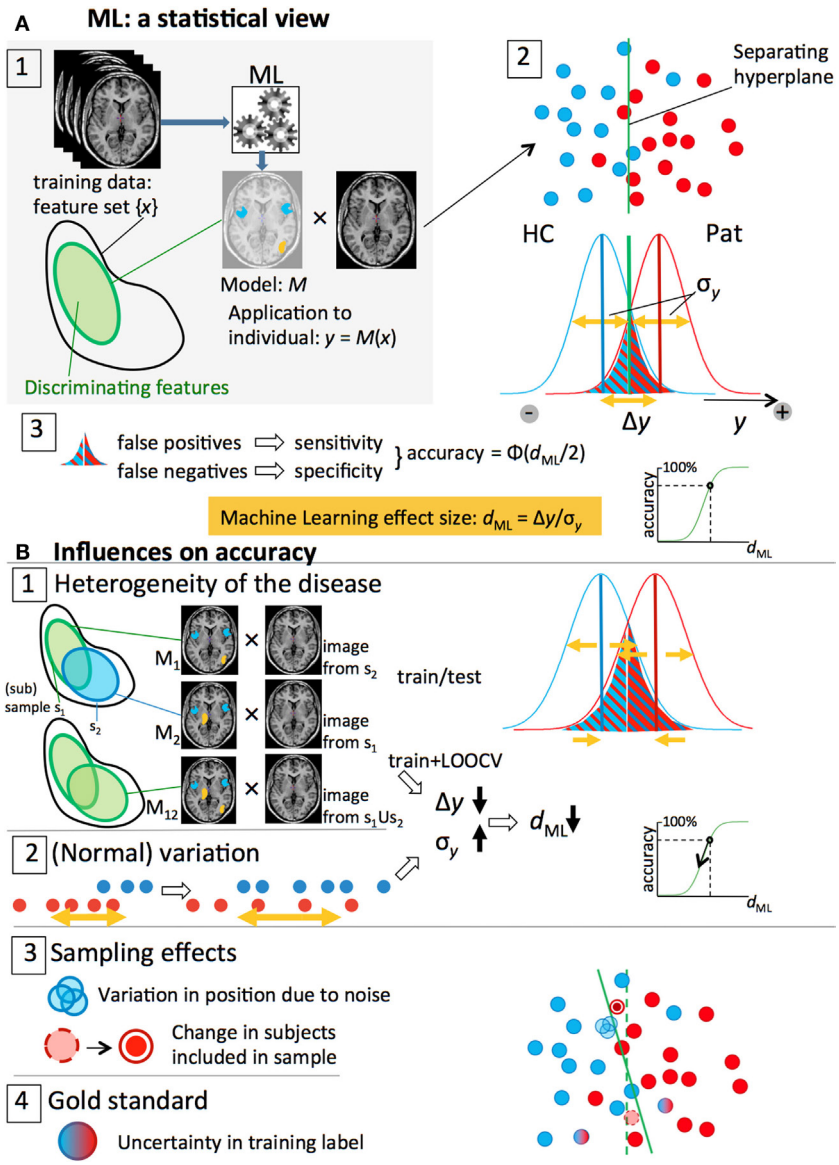

FIGURE 2 | Overview of the statistical side of machine learning in neuroimaging data and the different factors that influence prediction accuracy. **(A)** 1. An ML algorithm is trained on a set of labeled, preprocessed, MRI scans, resulting in a model M that classifies patients and controls based on a discriminative subset of the features (feature vector). 2. The classification is done by an (optimal) separating hyperplane in the (high-dimensional) feature space. Application of the model to an individual scan yields an output value y that is proportional to the distance of the subject's feature vector to the plane: blue (HC) and red (Pat) dots. The y-values of all subjects form two distributions with widths σ_y and means separated by a distance Δy. 3. A threshold halfway the distributions separates the two groups; the overlapping parts below and above the threshold represent the false negatives and false positive, respectively. For symmetrical distributions, the accuracy can be estimated from the ML effect size, $d_{ML} = \Delta y/\sigma_y$. **(B)** 1, 2. Heterogeneity of the disease and (normal) variation in brain measures lead to lower Δy and larger σ_y and, thus, smaller effect sizes and classification accuracies. 3, 4. Sampling effects and noise and imperfect expert labeling cause uncertainties in the positions of the subjects and affect the separating hyperplane and (test) accuracy.

(high-dimensional feature space) (**Figure 2A**-1). The features $\{x_i\}$ are distributed around a mean x with SD σ_x. In group-wise statistics, effect size Cohen's d is defined as $d = (x_1 - x_0)/\sigma_x$, which is a measure indicating how large the group-effect in this feature is in relation to the variation observed in this feature between subjects. The significance of this difference can be expressed by $t = d\sqrt{N}$ that can be converted to a p-value. From this formula, it is clear that, even for very small effect sizes d, a group difference can become "significant" by increasing N. This, however, has of course no effect on the overlap between the distributions. Suppose we would use this feature to separate the individuals of the two groups, we would draw a line as indicated in **Figure 2A**-2: the overlap of the distributions shaded in the Figure indicates the wrongly classified individuals. The non-overlap reflects the fraction of individuals that is correctly classified [Cohen's non-overlap measure U_2, see Ref. (20)]. Under the assumption that

the distributions of the feature are normal and equal for the two groups, this fraction may be estimated as $\Phi(d/2)$, where $\Phi(.)$ is the cumulative normal distribution (**Figure 2A**-3). While effect sizes of 0.8 and larger are commonly referred to as "large" (20) and would give rise to a "very significant" group difference $t = 8$ for $N = 100$, only 66% of the individuals would be assigned to the correct class in this case. This shows the fundamental difference between parameters that are significantly different between groups and their use for making individual predictions. This is one of the reasons that univariate prediction models are rare and that multivariate techniques are invoked to make use of the combined predictive power of many variables.

Machine Learning Effect Size

In the following, we will expand the univariate effect size to an effect size related to the output of multivariate ML models. Under application of a prediction model, a subject's feature set $\{x_i\}$ is transformed into a single value y, representing the outcome of the classifier (**Figure 2A**-1). For a binary classifier, values of $y > 0$ indicate a subject is classified as belonging to group "+1" (for instance, the patient group), and values of $y < 0$ indicate group "−1" membership (for instance, the control group). The distribution of $x \pm \sigma_x$ is transformed accordingly, yielding $y \pm \sigma_y$ (**Figure 2A**-2). In analogy to the group-level effect size, a ML effect size can be defined as $d_{ML} = \Delta y/\sigma_y$. Here, $\Delta y = y_1 - y_0$ is the "separation strength," i.e., the distance between the mean classification output values of the two groups, y_0 and y_1, respectively; the spread of the classifier's output around the group means is represented by σ_y, estimated as the pooled SD, $\sqrt{(\frac{1}{2}s^2_{y0} + \frac{1}{2}s^2_{y1})}$. The larger σ_y with respect to Δy, the more subjects will be wrongly classified (**Figure 2A**-3). The classification accuracy, defined as the fraction of correctly classified subjects, may, again, be estimated as $\Phi(d_{ML}/2)$ (**Figure 2A**-3). As we saw in the previous paragraph, "large" effect sizes (>0.8) will produce only moderate prediction accuracies (66% for $d_{ML} = 0.8$), which, from a diagnostic point of view, is not considered as being "large." A new scale should be defined for interpretation of ML effect sizes. For binary classification models, we suggest to label accuracies <60% ($d = 0.50$) as small; 60–70% ($d = 1.05$) as "modest"; 70–80% ($d = 1.68$) as "medium"; and >80% as "large" (see **Table 1**). In the following, we will identify the sources that influence prediction accuracy (via d_{ML}) that play a role in (neuroimaging) ML studies. This will help understanding the meaning of a certain published model together with its prediction accuracy.

Accuracy of ML Models: Gold Standard, Training, Testing, and Heterogeneous Samples

We will show that there are basically four "channels" through which the performance of a classifier is influenced (subsections 1–4; **Figures 2B**-1–**4**; **Table 2**). Depending on the kind of study and the way performance is assessed, different sources play a role. We present the ideas and some resulting formulas and numerical results for simple cases here. The derivation of the formulas is given in the Datasheet S1 in Supplementary Material. The results are then related to the observations made from **Figure 1**. To

TABLE 1 | Effect sizes, statistical and machine learning.

Effect size	Cohen's qualification	*t*/*p*		Machine learning	
		$N = 50$	$N = 200$	Accuracy (U_2, %)	Proposed qualification
0	–	0	0	50	
0.4	"Small"	1.41/0.16	2.83/0.005	58	"Small"
0.6	"Medium"	2.12/0.04	$4.24/3.10^{-5}$	62	"Modest"
0.8	"Large"	2.83/0.01	$5.66/<10^{-5}$	66	"Modest"
1.05–1.68	–	$3.71/5.10^{-4}$	$7.42/<10^{-5}$	70–80	"Medium"
>1.68	–	$5.94/<10^{-5}$	$11.9/<10^{-5}$	>80	"Large"

N is the total sample size; calculations assuming normally distributed data.

TABLE 2 | Factors that influence the ML effect size and classification accuracy.

Source	Relevant factor	Acting on	Effect in study:	
			Training + LOOCV	Train → test
Reference: homogeneous sample ("0")	Separation strength, Δy_0 Spread, σ_{y0}	–	$d_{ML0} = \Delta y_0/\sigma_{y0}$ $acc_0 = \Phi(d_{ML0}/2)$	–
Heterogeneity of the disease[a]	f	Separation strength, $\Delta y \rightarrow d_{ML}$	$d_{ML} = \sqrt{[(1 + f)/2]}\, d_{ML0}$	$d_{ML} = f d_{ML0}$
Heterogeneity: biological variation	σ_{BIOL}	broadening, $\sigma_y \rightarrow d_{ML}$	$d_{ML} = (\sigma_{y0}/\sigma_y) d_{ML0}$	$d_{MLT} = (\sigma_y/\sigma_{yT}) d_{ML}$
Measurement noise	σ_{EXP}	broadening, $\sigma_y \rightarrow d_{ML}$	$d_{ML} = (\sigma_{y0}/\sigma_y)\, d_{ML0}$	$d_{MLT} = (\sigma_y/\sigma_{yT}) d_{ML}$
Sampling effects (finite N)	N, σ_y	uncertainty in accuracy	≤ SD(acc) in train/test case	$SD(acc) = \sqrt{(acc_{true} \times (100\% - acc_{true})/N)}$
Gold → silver standard	Intra-class kappa, κ	ceiling of accuracy		$acc = \kappa \times acc_0 + (1-\kappa)/2$

[a]*i.e., related to the prediction model.*

$f = \cos(\theta)$, the relative amount of heterogeneity; $\sigma^2_y = \sigma^2_{BIOL} + \sigma^2_{EXP}$; acc = accuracy; subscripts "T" refer to values in the Test sample.

investigate the influence of the different sources, we will consider two types of ML prediction studies: (i) the single-sample study, where a model is trained and tested using (*k*-fold; leave-one-out) cross-validation (CV) in the same sample and (ii) the two-sample study where a model trained on one sample (the discovery sample) is tested in an independent second sample (the validation sample).

1. Heterogeneity of the Disease

Heterogeneity of the disease shows up as different parts of the brain being affected by the disease in different patients. This has a direct influence on the set of discriminating features and thus on Δy. Examples of source of disease heterogeneity are differences in: subtypes of the disorder (e.g., by symptoms, see Ref. (21)), disease status of the patients: illness severity (outcome) and course [age-of-onset and illness duration (first-episode patients versus chronic patients) and number of psychoses, etc.]; medication use [type and (cumulative) dose], etc.; differences in genetic background (as far as they influence the disease). However, much of the heterogeneity will not be attributable to clear factors. Disease heterogeneity has an effect in both the training sample (within-sample heterogeneity) and an independent test sample (between-sample heterogeneity).

1a. Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity

We start with training a disease prediction model in a homogeneous training sample (s_1, see **Figure 2B**-1). More precisely, strict inclusion criteria on the demographic and clinical parameters (e.g., age, gender, duration of illness) will lead to a clinically homogeneous sample. In such a sample, the disease-underlying brain abnormalities may be assumed to be as homogeneous as possible too. The prediction model (M_1) will find a "clear" discriminative pattern in these brain abnormalities and be able to transform the features $\{x_i\}$ into a decision value y that can separate the patients from the controls with high accuracy. Suppose we now wish to test the model's validity in an independent sample (s_2) that is derived from a different population and/or with different inclusion criteria (e.g., it has a different duration of illness or genetic background of the disease). Sample 2 is, thus, heterogeneous with respect to sample 1. Put differently, part of the (clinical) parameters is the same, but another part is different. The samples are said to be mutually heterogeneous, i.e., exhibit between-sample heterogeneity. We expect that this clinical heterogeneity is reflected by a heterogeneity of the underlying brain patterns too (**Figure 2B**-1). The model M_1 will not be sensitive to any brain abnormalities present in s_2 but not in s_1, and the part of the model that is based on abnormalities present in s_1 but not in s_2 will not contribute to the separation of cases and controls in s_2. Thus, only the pattern of shared abnormalities (the homogeneous part) will be of use for the classification of sample 2. For a linear prediction model M_1 and samples s_1 and s_2 that share a fraction f_{12} of discriminative features we can show that the separation strength in s_1, Δy, is in s_2 lowered according to this fraction: $f_{12}\Delta y$. The ML effect size is lowered by the same factor: $d_{\mathrm{ML}} \rightarrow f\, d_{\mathrm{ML}}$. In the range of 70–90% prediction accuracies for M_1, the resulting drop in accuracy in s_2 is approximately given by: $\Delta acc \approx 53\% \times {}^{10}\log f_{12}$ (see Datasheet S1 in Supplementary Material). For example, a 50% overlap in discriminative features between the samples ($f_{12} = 0.5$) will result in a drop of 16% classification accuracy in the test sample as compared to that obtained in the training sample.

1b. (Cross-Validation) Accuracy of the Model: Heterogeneity within Larger Training Samples

In Section "Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity," we considered the case of homogeneous samples. Such samples will be relatively small in practice. Larger samples will inevitably be heterogeneous because of the difficulty to include a large amount of subjects fulfilling the strict inclusion criteria. In the following, we will assume that this heterogeneous sample is constituted of two or more homogeneous subsamples. Part of the properties is shared between the subsamples, but other properties differ (e.g., duration of illness). For the case of two subsamples, the situation is the same as described in the previous section (**Figures 2B**-1 and **3A**), but now a model M_{12} is trained on the combined $s_1 + s_2$ sample. The model will be a weighted average of the (hypothetical) models from the homogeneous subsamples. The amount of within-sample heterogeneity is determined by both the number of homogeneous subsamples the sample can be divided into and the overlap between the discriminative feature sets (**Figures 2B**-1 and **3A,B**). The larger the within-sample heterogeneity, the lower the separation strength Δy will be (*cf,* see Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity). Furthermore, different sets of discriminative features will generally also lead to a larger pool of discriminative features that will not contribute to the discrimination in most subjects but will have random effects (affecting σ_y). The net effect is a decrease of the effect size d_{ML}. Training (CV) accuracy will be lower as compared to a (hypothetical) homogeneous sample (of the same size) and depend on the within-sample heterogeneity, which, for a two-subsample case is defined by the fraction of shared features, f_{12}. The effect size is attenuated as follows: $\sqrt{((1 + f_{12})/2)}$. (See section C of the Datasheet S1 in Supplementary Material for the derivation of this formula and section F for numerical simulations to test it.) When applied to an independent sample, the test accuracy of the model depends on the between-sample heterogeneity (as discussed in Section "Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity"). For a sample consisting of two homogeneous subsamples s_1 and s_2, the accuracy drop is in the range 70–90% approximately given by: $\Delta acc \approx 26\% \times {}^{10}\log((1 + f_{12})/2)$, as compared to the accuracy in sample s_1 or sample s_2 alone.

These formulas can be extended to samples with H-fold within-sample heterogeneity ($H \geq 2$, see **Figure 3C**) leading to larger drops in accuracy. The reader is referred to the Datasheet S1 in Supplementary Material for the corresponding formulas. Note that thus far we treated the heterogeneity as being

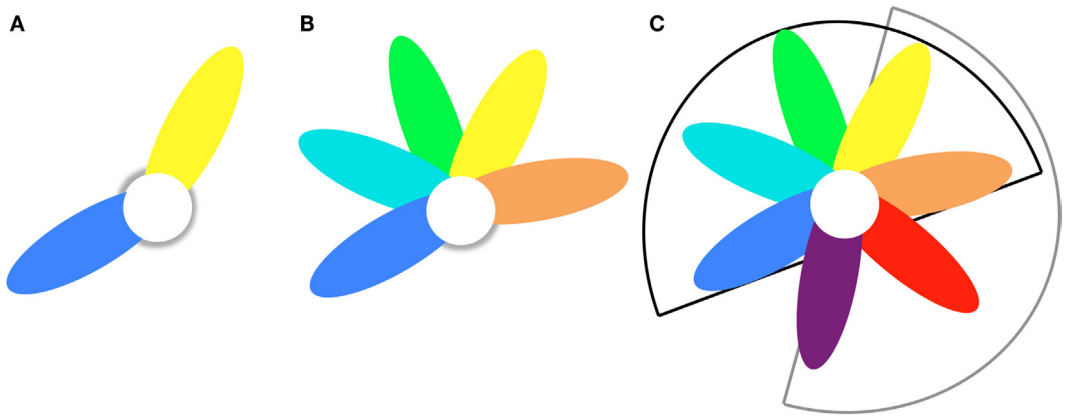

FIGURE 3 | Petal model to describe disease heterogeneity within and between samples. **(A)** Two-fold heterogeneity sample consists of blue and yellow subsamples that have shared (white) and unique (colored) brain abnormalities. **(B)** *H*-fold heterogeneity sample consists of $H = 5$ subsamples that have shared (white) and unique (colored) brain abnormalities. **(C)** Train/test heterogeneity The model trained on sample B ($H = 5$; black sector) is tested on a sample with H'-fold heterogeneity ($H' = 4$; grey sector). The overlap is *T*-fold ($T = 2$; yellow and orange petals).

discrete ($H = 2,3,\ldots$). While this may be a good description for disease heterogeneity related to, e.g., gender, in general the heterogeneity will probably have a continuous nature. For instance, first-episode versus chronic is not a hard cut, but is described by the continuous parameter illness duration. This can be incorporated in the formulas by allowing *H* to assume non-integer values.

2. Variation

2a. Non-Disease-Related Heterogeneity

Heterogeneity with respect to factors not related to the disease gives rise to variation in brain measures (**Figure 2B**-2). This biological variation is present in both healthy subjects and patients. The more heterogeneous a sample is, the larger the variation in feature values. Examples are as follows: including males and females (as opposed to single-gender); including subjects with a wide age or IQ range; genetic background (but for genetic disease-related genetic factors, see Heterogeneity of the Disease). Relaxing the inclusion criteria of a study will thus increase the variation in feature values $\{x_i\}$.

Matching of subjects with respect to nuisance variables: Confounding the classifier

A special form of increased variation arises when subjects are not well-matched with respect to nuisance variables. If the distributions of factors such as age and gender are not well-matched between train and test samples, (parts of) the classifier's output distribution (y) may shift, causing a change in the sensitivity/specificity balance. Within-sample mismatch with respect to nuisance variables between patients and controls will confound the classifier: part of the discrimination between the two groups will be based on brain abnormalities unrelated to the disease. For instance, if the patients are on average older than the controls, brain volume decreases related to normal aging may be used by the classifier to separate the groups. When applied to a test sample with a different demographic composition, this part of the model will not contribute to the separation of the groups, and the effect size will be lowered by a factor $f < 1$ (see Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity).

2b. Measurement Noise

The second factor that increases the variation in feature values $\{x_i\}$ is measurement noise (**Figure 2B**-3). Features are derived from measurements done by, e.g., an MRI scanner, which inherently involves noise. Random noise, such as, e.g., physiologic and electronic noise and noise due to subject movements, leads to an uncertainty in the feature values. Systematic (and interaction) effects, due to differences in, e.g., scanner brand and type, field strength, and acquisition protocols, play a role when two or more samples with different origin are combined, e.g., in a train/test study. These effects can result in biased sensitivity/specificity (e.g., when certain parts of the brain show up differently between two scanners) or in changes in the prediction accuracy (which will be lower for noisier scans, but could even go up if test scans were acquired with less noise, e.g., on a scanner with higher field strength).

While variation due to inclusion of biologically heterogeneous subjects (see Non-Disease-Related Heterogeneity) and Section "measurement noise" is completely different in nature, their effects on the ML accuracy run via the same channel: increased variation in the features $\{x_i\}$, which is carried over to the variance of the prediction model's output: σ_y. The total variance is given by: $\sigma^2_y = \sigma^2_{\mathrm{BIOL}} + \sigma^2_{\mathrm{EXP}}$. Lower or higher variance (σ_y) in the test set as compared to the training set can cause increases or decreases (respectively) in the test accuracy, according to the same formula as used in Section "Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity," since it is determined by the effect size $d_{\mathrm{ML}} = f\Delta y/\sigma_y$. A twice as large noise will have the same effect as a 50% overlap.

3. Sampling Effects (Finite *N*)

In samples of finite size, random variations influence both the modeling (training phase) and the testing. Two effects play a role here.

3a. Train/Test Case

First, if we assume that a theoretical, population-based, model exists, then in practice a model will depend on the actual training sample taken from "the population." Differences in the amount and kind of heterogeneity in the selected subjects will cause both differences in prediction accuracy and "positioning" of the model [optimal separation hyperplane (OSH)] with respect to the population-based model. Models "further away" from this population-based model will more likely perform worse (i.e., producing lower accuracies) in a second, independent test sample from the same population. The accuracy in test samples is, thus, hit twice by the sampling effect: once due to fluctuations in the test sample's composition itself (having a lucky or an unlucky drawing of subjects with respect to the population distribution) and a second time because of the composition of the training sample, on which the model was built (relative position of the two samples). This effect is larger in smaller (training and testing) samples. The observed accuracies officially follow a binomial distribution, but can be approximated by a normal distribution with mean acc_{true} and an SD of $\sqrt{(acc_{\text{true}} \times (100\% - acc_{\text{true}})/N)}$. For an acc_{true} of 80%, SD = 40%/$\sqrt{N}$, thus in a sample of $N = 50$ (25 + 25 per group), SD = 5.7%, giving a chance of 95% that the observed *acc* lies between 68.6 and 91.4%. For four times as large sample, $N = 200$, this range is 74.3−85.7%. Note that the sampling effect, thus, does not systematically lower the accuracy, but that it gives rise to variation in it. It is true, however, that the lower the *N*, the larger the chance of observing a low accuracy (as well as a high accuracy).

3b. Cross-Validation Case

Second, if performance is tested within the training set, CV will induce small perturbations in this set during each step of the leave-one(or more)-out procedure, accounting for further fluctuations around the "theoretical" OSH (**Figure 2B**-3). The effect on the (CV) accuracy is difficult to estimate, since it will depend on the type of classifier used. For example, a support vector machine (SVM) model is based on only part of the training subjects [the so-called support vectors (SV)], who are recognized as lying close to the OSH during the training phase. Leaving-out a non-SV subject will not influence the model, while leaving out a SV subject probably will change the placement of the OSH and, thus, the classification of subjects nearby the OSH. If the number of support vectors (N_{SV}) is known, a reasonable estimate of the SD of the accuracy could be made by the formula for SD in the previous paragraph, using N_{SV} instead of *N*.

Note that sampling effects induce spread in accuracy, but not a reduction of it *per se* (although the spread distribution becomes asymmetric for population-based accuracies above 50%, the expectation value of the accuracy in a sample always equals the accuracy in the population). However, since the spread is larger for lower *N* and (accidently) low accuracies are less likely to be published, the sampling effect may add to the on average higher accuracies in low-*N* studies.

An illustration of the sampling effect as a function of training sample size *N* can be found in Ref. (11). In their **Figure 3,** the rise of the mean accuracy with *N* reflects a training sample-based OSH that lies closer to the population-based OSH [see Train/Test Case]. The lower spread in observed accuracies with increasing *N* (light blue circles) reflects the decreasing SD [see Cross-Validation Case]. Of course, the fact that these effects occur is a reflection of the disease heterogeneity (see Heterogeneity of the Disease) and biological variability (see Variation) present in the sample: without variability sampling effects do not play a role.

4. Training: From Gold to Silver Standard

Last but not least, in a supervised learning study, the quality of the expert labeling of the subjects in the training set (and, in fact, in the test set too) influences the highest possible accuracy. Unfortunately, especially for prediction problems in psychiatry, the reliability of the experts may not always be that high [see Ref. (22), for a study on reliability of DSM-5 diagnoses, using interclass kappa (23)]. This means that, in many cases, we have, unfortunately, not a gold, but rather a silver standard (**Figure 2B**-4). The quality of the standard is different for different classification problems, and may be close to 0 in certain situations, but for diagnosis of SZ and bipolar disorder using SCID-I inter-rater reliabilities of 80–94% has been found (24) and using DSM-5 interclass kappa's of 0.46–0.56 (22). In general, a drop of ~10% can safely be assumed. Of course, 100% accurate training models can still be obtained, but there is a hidden inaccuracy due to subjects wrongly labeled by the expert. While this inaccuracy goes unnoticed in the training results, it will at any rate be revealed in the test phase, either by CV or in a test sample. Although mislabeling by the expert may be linked to the more difficult cases, ignoring this leads to a simple formula for a two-class test case: $acc = \kappa \times acc_0 + (1 - \kappa)/2$, which is smaller than the true accuracy (acc_0) for $acc_0 > 50\%$; κ is the interclass kappa, which, for a two-class/two-rater case can be related to the fraction of cases mislabeled by the experts: $(1 - \kappa)/2$. This formula could even be extended for estimating the loss of accuracy in the CV in the training sample, but this depends on the type of classifier. The CV procedure is hit twice by errors in the expert labeling: when the left-out subject is predicted (as described above), but also when the model is built. If all subjects influence the model, the effect is about the same as in the test phase. If, however, as e.g., SVM, only part of the subjects (N_{SV}) actually influences the model, a mislabeled non-SV subject has no influence. On the other hand, probably the subjects close to the separation border, the SVs, are also the ones that are most difficult to be classified by the expert.

Summary

To summarize (see **Figures 4A–E**), imperfection of the gold standard (**Figure 4A**) will lower the ceiling of the training accuracy (ideally, 100%) in the training set [silver standard (**Figure 4B**)]. (Within-sample) disease-pattern heterogeneity will introduce the impossibility to capture all discriminating brain abnormalities needed for the classification of all subjects, thus reducing the accuracy (**Figure 4C**). Finite sample sizes and biological variation and measurement noise will lower the (*k*-fold; leave-one-out) CV

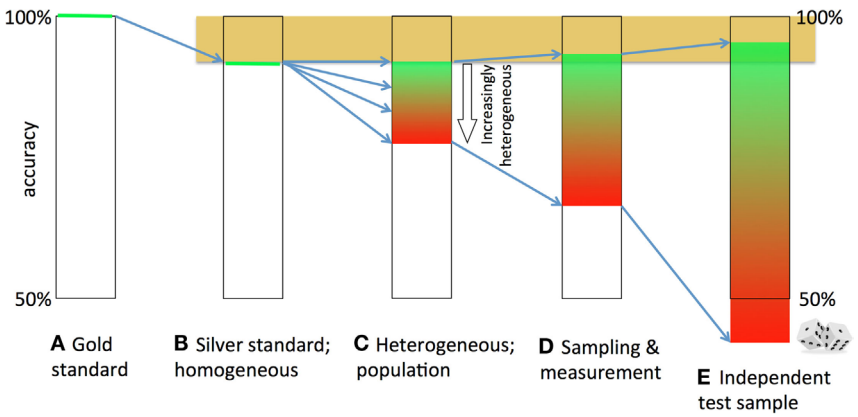

FIGURE 4 | Decay and broadening of the prediction accuracy. The theoretically attainable 100% accuracy **(A)** is lowered, because the gold standard is imperfect **(B)**. If the brain abnormalities underlying the disease are heterogeneous, no straightforward (linear) model can classify all patients correctly **(C)**. Sampling effects, biological variation and measurement noise further lower and broaden the accuracy **(D)**. Finally, if a model is tested in an independent sample, the accuracy becomes lower due to between-sample heterogeneity and broader due to sampling effects **(E)**.

accuracy further (**Figure 4D**). In an independent test sample, when the model is applied to a new data set, this negative effect of (between-sample) heterogeneity on the prediction accuracy will be magnified, and sampling effects will cause further spread in the test accuracy (**Figure 4E**). The loss will depend on the overlap in discriminative features between train and test sample, or, the between-sample disease-pattern heterogeneity.

Relationship between the Heterogeneity Factor "f" and the (Feature) Weight Vectors, Cos(θ): The Angle of Heterogeneity

In linear models, such as, e.g., the linear SVM, the model can be represented by a set of coefficients, β, or weight vector w, indicating the features' relative importance. The decision value y is the dot product of this vector and the feature vector: $y = w^{T}.x$ (offset b is not relevant here). When comparing two models, the dot product of the (normalized) weight vectors can be informative: it provides a summary statistic of the comparability of the two models. It can be shown (see Datasheet S1 in Supplementary Material) that the disease heterogeneity factor $f = \cos(\theta)$, the dot product of the normalized weight vectors. θ is the angle between the two vectors (or, equivalently, the separating hyperplanes): the angle of heterogeneity. In this context, it should be noted that disease heterogeneity can arise in two forms. Thus far we split discriminative features in a part shared by subgroups of patients and in features specific to each of the subgroups (and, thus, absent in the other subgroups). It is, however, also possible that certain features are discriminative in more than one subgroup, but in different directions: for instance, a piece of the cortex that is either too thin or too thick could be disadvantageous and, thus, related to having the disease. Such manifestations of heterogeneity of the disease could lead to angles larger than 90° and, thus, negative f. The values f can assume are, thus, between −1 and +1. While f, or cos(θ), thus provide an indication of the global comparability between two models, detailed information needs to be obtained by comparison on a weight-by-weight basis, e.g., by comparing projections of the weight vectors on brain maps.

Application to the Published sMRI-ML Schizophrenia Studies

Figure 1 shows the derived effects in relation to the published sMRI-ML studies in SZ.

The heterogeneous-sample model has been "fitted" to the data points representing CV studies, using parameter values of ($d_0 = 2.00$; $f_{12} = 0$; $N = H \times N_0$; $N_0 = 50$). Note that this "fit" is descriptive (i.e., no rigorous optimization of the goodness-of-fit with optimal parameter estimates and confidence intervals was carried out): the line is an indication of how the fall of the accuracy with sample size can be explained by increasing within-sample heterogeneity. We assumed constant values for the homogeneous-sample ML effect size d_0, the (within-sample) heterogeneity factor f_{12}, and the homogeneous-subsample size N_0, but these values can, of course, vary between the studies. For smaller samples (up to $N \approx 60$), the accuracy seems to lie at a plateau (~90%). This could indicate that researchers have been able to stretch the maximum sample size that allows the inclusion of patients with homogeneous disease-related brain abnormalities. The ~90% ceiling of the accuracy probably reflects the maximum possible accuracy that can be obtained with imperfect gold standard (see Training: From Gold to Silver Standard).

Four studies tested their HC/SZ classification model in an independent validation sample. Two small studies obtained test accuracies that were even higher than the train accuracies, which is probably due to the effect of sampling [having a lucky drawing in the test sample; Section "Sampling Effects (Finite N)"], which is larger for low N. The 7% jump in accuracy (from 77% in the training set to 84% in the test set) found by Kawasaki et al. (25) is of the order of the uncertainty in the accuracy, SD = 5–7%, for these sample sizes ($N = 30 + 30$ and $N = 16 + 16$, respectively).

The other possible cause, better image quality in the test set, seems not applicable here, since both sets were drawn from the same cohort. The study by Iwabuchi et al. (19), on the other hand, clearly shows the effect of scan quality: Using the same sample, they built two classification models: one based on 3-T scans and one based on 7-T scans. While increasing field strength does not automatically lead to improved scan quality, higher resolution or better contrast-to-noise ratio is usually obtained. Indeed, the accuracy increased from 67% in the 3-T models to 77% in the 7-T models. (Note that sampling effects do not play a role here, since the same subjects were used for both models.)

Two other (smaller-sized) studies displayed a large drop (>10%) of accuracy in the test sample as compared to the train sample; note that the $N/2 = 66$ study used a test set acquired at different field strength (3 T versus 1.5 T). This can be explained by the fact that low-N training samples can be more homogeneous, giving rise to (i) the higher CV accuracies (>88%) seen here [see (Cross-Validation) Accuracy of the Model: Heterogeneity within Larger Training Samples] and (ii) a larger mutual, or between-sample, heterogeneity with the test sample, yielding larger drops in accuracy (see Testing a Model's Accuracy in an Independent Validation Sample: Heterogeneity in the Population, Causing between-Sample Heterogeneity). Of course, sampling effects could also add to the large differences here. The only large train/test study ($N/2 = 120$) showed almost no (1%) drop in accuracy between train and test sample. This is in agreement with the theory that larger studies automatically capture more (within-sample) disease heterogeneity and, thus, better generalize – at the cost of lower accuracy. For three train–test studies, the overlap in discriminative features could be estimated, with relatively low values of $f_{12} = 0.6$, for the smaller studies, and a high value for the larger study: $f_{12} = 0.95$.

The study by Nieuwenhuis et al. (11) reported a full model (presented in **Figure 1**) and two sub-models. The first sub-model excluded the striatum, known for being affected by typical antipsychotics (26), from the feature set. Half of the patients in the training sample were on typical antipsychotics, and as could be seen from their **Figure 2**, the discrimination between patients and controls was in part based on gray matter differences in the striatum. Excluding the striatum leads to a 4% reduction in classification accuracy. This drop could be attributed to less discriminative information being present in the sample and, thus, a drop in "separation strength" Δy (see Heterogeneity of the Disease) and ML effect size d_{ML} and accuracy for the discovery sample. However, since hardly any patients (8%) of the validation sample were on typical antipsychotics, the part of the model based on the medicated striatum was of no discriminating value for this sample and, thus, nothing changed for the validation performance (+0.2%). [The striatum features were located in the s_1-petal (**Figure 3A**).] The second sub-model was trained on the top-10% features with the largest absolute weights. The CV accuracy of this model increased to 86.8%, probably because the other 90% of the features did not contribute much to the discrimination (separation strength Δy hardly changed) but did add quite some noise: the spread in predictions, σ^2, decreased and the ML effect size d_{ML}, thus, increased. This model, however, was apparently more tuned ("overfitted") to the specific constitution of the training sample with respect to its disease heterogeneity (i.e., the petals in **Figure 3** had become relatively large as compared to the core), and thus the improved prediction accuracy was not found again in the validation sample, which had an almost unchanged accuracy of 69.1%.

DISCUSSION

In this work, we examined the various sources that influence the performance of ML classification and prediction studies in psychiatric neuroimaging. The published studies on the prediction of SZ using sMRI display a wide variation in classification accuracies. From a plot of accuracy versus sample size (**Figure 1**), we showed that the accuracy of these classification studies drops from a plateau at about 90% in smaller samples ($N/2 <$ ~60) to (below) 70% for studies with larger N. A simple heterogeneous-sample model was able to follow this drop in (maximum) accuracy with increasing sample size. Smaller studies are better capable of including homogeneous samples, which allow for the discovery of discriminative brain features that apply to all patients, yielding models with high accuracy. Larger studies inevitably need to relax the inclusion criteria, yielding heterogeneous samples in which no discriminative pattern of brain abnormalities can be found that is shared by all patients. As a result, only part of the subjects will be correctly classified, resulting in lower accuracy.

Application of these classification models to independent validation samples allows for testing their generalizability. From the few studies that performed such a test, it was observed that accuracy can drop as much as 10–15% or even can increase for the smaller studies. The only study with large train/test samples showed a much more stable accuracy (a drop of only 1%). Patients in a test sample will most likely display a different pattern of brain abnormalities as compared to those in the training set, i.e., the two samples are mutually heterogeneous. The accuracy in the replication sample will be (much) lower, depending on the amount of shared features between the two samples. The drop in accuracy will presumably be smaller for studies with a large training sample, since it will automatically cover more disease features from the set of all possible features.

An additional advantage of larger studies is that they are less prone to sampling effects. The larger variability in accuracy, which is observed for smaller studies, could be explained by lucky/unlucky drawings from the patient population.

Summarizing, sample size influences the trade-off between accuracy and generalizability. Smaller, homogeneous, samples are able to produce classification models with high accuracy, at the cost of low generalizability, whereas larger, heterogeneous samples produce models that better generalize, but at the cost of lower accuracy. We argue here that, with the current approaches, high accuracy cannot be reached in larger, heterogeneous samples – in psychiatry. From an evaluation of the ML literature on neurological diseases (10), it is noted that ML studies on Alzheimer's disease seem to reach high accuracy from small N till very large N. This may be attributed to the more precise characterization of

this disease, thus leading to a more homogeneous population and thus samples. Studies on mild cognitive impairment, on the other hand, do show a substantial drop in accuracy with N, probably because this class of patients is less well defined, and thus leading to increased (within-sample) heterogeneity.

The spread in accuracy seen in first-episode SZ (FE-SZ) ML studies could have two causes. On the one hand, the FE-SZ class of patients does show some variability in presentation and clinical course, but is, compared to a chronic/mixed group of patients, more homogeneous [shorter duration of illness; less variability in age and disease course; less (variation in) (cumulative) medication (dose); etc.] allowing for higher accuracy. On the other hand, the disease effects in the brain may be smaller in these patients than in chronic patients, lowering the separability of the groups. Both effects influence the ML effect size and, thus, the model's performance. Spread in inclusion criteria between studies, for instance, with respect to illness duration, can have led to differences in effect sizes between the FE-SZ studies. Given the difficulty to include large number of FE-SZ subjects, all FE-SZ ML studies were relatively small ($N/2 < 65$). Sampling effects could also contribute to the large variation in accuracies, for these relatively low numbers of subjects.

There are many possible sources of heterogeneity. Psychiatric disorders may be divided into subtypes (see, e.g., Ref. (21) for SZ). Within "homogeneous subtypes," the disease status of patients plays a role: illness severity (outcome) and course (age-of-onset and illness duration; number of psychoses, etc.); medication use [type and (cumulative) dose], etc. Furthermore, even a "clinically" homogeneous patient group may show heterogeneity in their underlying brain abnormalities, because, e.g., different (disease-related) genetic factors may cause different biological pathways to the same (subtype of the) disease. Nuisance variables also further increase a sample's heterogeneity, because of (normal) variation in brain tissue properties related to age, gender, IQ, and so on. Apart from all these biological factors that influence "true" heterogeneity, experimental heterogeneity is introduced by, e.g., scanner effects.

Although we can explain the observed accuracy distributions both qualitatively and quantitatively to large extent by (disease) heterogeneity and sampling effects, it should be noted that there are other possible explanations as well. Lower (CV) accuracy could simply reflect a worse model due to reasons, such as poorer quality of the input data, for instance, due to scan quality (acquisition, subject motion), image preprocessing, or choices made regarding the kind of features (e.g., high-resolution gray matter volumes may be more discriminative than mean-FA values in the fiber tracts). Other possible causes include a less fortunate selection of features or suboptimal modeling methods (e.g., choice of ML type or parameter settings).

While from these observations the picture may arise that studies employing both large (training) samples and independent validation samples are most powerful and informative, studies with smaller N are as useful for the understanding of the biological background of the disease for several reasons. If a small N study included an application of the model to an independent replication sample, the drop in accuracy carries information about the (mutual) homogeneity of the sample. In fact, if the study has the disposal of two independent samples, two models should be trained on each sample separately, which should be tested on the other sample. This cross-sample application provides information about the within- and between-samples heterogeneity and allows for comparison of the separating brain patterns, yielding shared and sample-specific discriminative brain features. In a later stage, the results of studies could be combined for the same purpose: mapping the variability (in populations) of underlying brain patterns for classification and prediction of psychiatric disorders. For example, ML brain patterns from medication naïve patients could be compared to those from medicated first-episode patients. Special populations for which it is difficult to acquire large samples can provide biomarker information that is specific for that population. To get the most out of such samples, both as a single study and in possible later multi/cross-center studies, it is important to have as much as possible demographic and clinical information available.

In order to interpret the published studies and value them for use in cross-study application, it is thus important that details of the analysis and results are reported. For instance, in SVM studies, the number of subjects the model is based on, i.e., the N_{SV}, could be provided. As an example, the SZ classification model by Nieuwenhuis et al. (11) was based on $N_{SV} = 257$ out of $N = 294$ subjects in total. The relative large number of SVs (87%) could reflect the large heterogeneity of the training sample. Likewise, in a (M)LDA approach (see, e.g., Ref. (27)), the number of eigenvectors used in the model could be reported.

Limitations

In this work, we described the factors influencing ML model performance qualitatively and quantitatively. For the quantitative description, there was only room here to treat the most elementary form of sample heterogeneity and its effect on linear prediction models. We believe, however, that it covers the principle of disease heterogeneity to "first-order approximation." The theory should be extended to include refined descriptions of sample heterogeneity and the effects in other ML setups: non-linear models, more than two classes, prediction of continuous measures, such as disease course (outcome) and so on. The ML effect size could be extended beyond the discrete, binary, case. Systematic (scanner etc.) effects were ignored, which will influence sensitivity and specificity in a different way. The implications of sample heterogeneity were mostly discussed within the framework of linear classifiers, and in particular the linear SVM. The theory should be broadened to other types of ML such as Gaussian Processes (28) and (M)LDA (27), and non-linear classifiers. Non-linear classifiers might be better capable of modeling the heterogeneity, but are more prone to overfitting, thus possibly reaching higher accuracies in the training sample, but which are less generalizable to other samples. However, using much larger (multicenter) samples may (partly) overcome this drawback. (Group-level-based) feature selection may reduce heterogeneity of the features, while using lower-dimensional brain features, e.g., by taking ROI-based measures instead of voxel/vertex-based measures or by applying principal component analysis (PCA) to

the high-dimensional brain data, could have the same effect. While this may increase the robustness of the models, they will less well incorporate the variation in disease-related brain abnormalities, thus, probably not be able to reach high generalization performance.

In conclusion, the wide variation in observed prediction accuracy in this young field of research is an indication that the ML models are built on samples that are mutually very different. Disease heterogeneity, (normal) biological variation, noise and sampling effects, and imperfect expert labeling influence the results. Sample size and observed accuracy can be translated into information about the within- and between-sample heterogeneity, which, in turn, could be interpreted in terms of the sample characteristics, if provided. The meaning of a study's accuracy is limited if it cannot be connected to the study design and characteristics of the sample. Pursuing a high accuracy should not be a goal in its own if we aim to increase the knowledge about the biological background of the disease. Furthermore, one should be cautious with statements about the potential clinical use of some prediction model, even if it yielded high prediction accuracy. Accuracy is a relevant measure, but only in combination with a detailed description of the sample and design of the study it gives us valuable information.

For the next generation of ML studies in psychiatric imaging to be as fruitful as possible, we would recommend the following:

1. The report of more details of the sample(s) and ML analysis.
   (a) Regarding the sample(s): as much as possible information about the sample should be provided: demographic and clinical parameters: distribution of gender, ethnicity, (range and mean, SD of) age, IQ, socioeconomic status, geographical background, etc.; duration of illness/age of onset, (dose and type of) medication, scores of functioning and outcome, and so on. Furthermore, neuroimaging parameters, such as MRI acquisition and preprocessing details should be provided.
   (b) Regarding the modeling: (i) inputs and settings: these details include type and number of features in the (final) model; parameter settings (e.g., C in linear SVM); (ii) relevant properties of the resulting model, when possible, such as (pictures of) weight vectors (weight maps) and their significance, and, in SVM, e.g., the N_{SV}.
   (c) Regarding the model's performance: balanced (or total) accuracy, sensitivity and specificity (or, equivalently, positive and negative predicted values), and the area under the curve (AUC) from a receiver operating curve (ROC) analysis, that, in itself, provides more insight into the balance between sensitivity and specificity at different thresholds. Furthermore, the resulting effect size (d_{ML}), calculated from the separation strength (Δy) and SDs of the mean y, for each of the classes (groups) should be reported, as well as the effect size calculated from the AUC (see Datasheet S1 in Supplementary Material section G for formulas and a Matlab script). For ML algorithms that do not produce "about-normally" distributed output (e.g., voting), the ML effect size could be estimated by calculating $2 \times \Phi^{-1}(acc)$. Bootstrap analyses enable the estimation of uncertainties in the estimated d_{ML}'s and accuracies and resulting p-values and confidence intervals.
2. Additional modeling. The performance of the (final) model could be improved by applying model averaging, such as (su) bagging, lowering the variance of the model's output (29). Submodelings, e.g., with different selections of features, related to the parameters described in point 1, could shed more light on the relationship between certain features and subgroups of subjects. An example is the modeling of males and females separately. Apart from these extra models, the performance of the final model on these subgroups itself already provides insight into possible interactions between, e.g., gender and classification.
3. Use large (single-center) samples to build classification models: they automatically cover more variation in the disease features (and are less influenced by accidental variations and noise) and, thus, more robust (for application to other samples).
4. Validation. If possible, always use a training sample and an *independent* replication sample. Independency here means that the subjects were at least not acquired as part of the first study.
5. Apply cross-center validation. Models built in one site could be tested in the other, and vice versa. This is an extension of point 4. Do not be afraid of substantial losses in accuracy: they carry information about the overlap in disease features. Further extending this line of thought is the possibility to build prediction models from multicenter data; technical (scanner) and clinical (diagnostic) differences may somewhat degrade the performance, but the shared disease factors will survive (30). Recently, multicenter consortia have recently been initiated to investigate the possibility of translating neuroimaging findings into clinical practice (IMAGEMEND[1] PRONIA[2] and PSYSCAN[3]).

AUTHOR CONTRIBUTIONS

HS and RK made substantial contributions to the conception (RK) and design (HS) of the work and the analysis and interpretation (HS) of the data. HS drafted the work and RK revised it critically. HS and RK gave final approval of the manuscript. HS and RK agree to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2016.00050

[1] http://www.imagemend.eu
[2] www.pronia.eu
[3] www.psyscan.eu

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

CASE REPORT
published: 15 March 2016
doi: 10.3389/fpsyt.2016.00037

Targeting Treatment-Resistant Auditory Verbal Hallucinations in Schizophrenia with fMRI-Based Neurofeedback – Exploring Different Cases of Schizophrenia

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OPEN ACCESS

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: 11 December 2015
Accepted: 29 February 2016
Published: 15 March 2016

Citation:
Dyck MS, Mathiak KA, Bergert S, Sarkheil P, Koush Y, Alawi EM, Zvyagintsev M, Gaebler AJ, Shergill SS and Mathiak K (2016) Targeting Treatment-Resistant Auditory Verbal Hallucinations in Schizophrenia with fMRI-Based Neurofeedback – Exploring Different Cases of Schizophrenia. Front. Psychiatry 7:37. doi: 10.3389/fpsyt.2016.00037

Auditory verbal hallucinations (AVHs) are a hallmark of schizophrenia and can significantly impair patients' emotional, social, and occupational functioning. Despite progress in psychopharmacology, over 25% of schizophrenia patients suffer from treatment-resistant hallucinations. In the search for alternative treatment methods, neurofeedback (NF) emerges as a promising therapy tool. NF based on real-time functional magnetic resonance imaging (rt-fMRI) allows voluntarily change of the activity in a selected brain region – even in patients with schizophrenia. This study explored effects of NF on ongoing AVHs. The selected participants were trained in the self-regulation of activity in the anterior cingulate cortex (ACC), a key monitoring region involved in generation and intensity modulation of AVHs. Using rt-fMRI, three right-handed patients, suffering from schizophrenia and ongoing, treatment-resistant AVHs, learned control over ACC activity on three separate days. The effect of NF training on hallucinations' severity was assessed with the Auditory Vocal Hallucination Rating Scale (AVHRS) and on the affective state – with the Positive and Negative Affect Schedule (PANAS). All patients yielded significant upregulation of the ACC and reported subjective improvement in some aspects of AVHs (AVHRS) such as disturbance and suffering from the voices. In general, mood (PANAS) improved during NF training, though two patients reported

Abbreviations: ACC, anterior cingulate cortex; AC–PC, anterior commissure–posterior commissure; AVHRS, Auditory Vocal Hallucination Rating Scale; AVHs, auditory verbal hallucinations; BOLD, blood-oxygen-level dependent; DBS, deep brain stimulation; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; ECT, electroconvulsive therapy; EEG, electroencephalography; EPI, echo planar imaging; FEW, family-wise error; MNI, Montreal Neurological Institute; NF, neurofeedback; PANAS, Positive and Negative Affect Schedule; PANSS, Positive and Negative Syndrome Scale; PTSD, post-traumatic stress disorder; ROI, region of interest; rt-fMRI, real-time functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; SCID-I, structured clinical interview-axis I; SPM, statistical parametric mapping; STG, superior temporal gyrus; tDCS, transcranial direct current stimulation; TR, repetition time.

worse mood after NF on the third day. ACC and reward system activity during NF learning and specific effects on mood and symptoms varied across the participants. None of them profited from the last training set in the prolonged three-session training. Moreover, individual differences emerged in brain networks activated with NF and in symptom changes, which were related to the patients' symptomatology and disease history. NF based on rt-fMRI seems a promising tool in therapy of AVHs. The patients, who suffered from continuous hallucinations for years, experienced symptom changes that may be attributed to the NF training. In order to assess the effectiveness of NF as a therapeutic method, this effect has to be studied systematically in larger groups; further, long-term effects need to be assessed. Particularly in schizophrenia, future NF studies should take into account the individual differences in reward processing, fatigue, and motivation to develop individualized training protocols.

Keywords: schizophrenia, auditory hallucinations, functional magnetic resonance imaging, neurofeedback, brain–computer interface, self-regulation, anterior cingulate cortex, affect

INTRODUCTION

Auditory verbal hallucinations (AVHs) are a hallmark of schizophrenia and affect approximately 60–80% of patients with schizophrenia (1). They encompass a range of experiences: single or multiple voices; familiar to the patient or unknown; speaking sequentially or simultaneously; speaking in the first, second, or third person; giving commands, comments, insults, or encouragement (2). AVHs constitute a significant persisting burden for the patients (3) and are typically associated with social and occupational dysfunction (4) as well as worse prognosis (5). A large meta-analysis (6) revealed that only 14% of individuals with schizophrenia fully recover over 10 years. The rest will suffer from negative and positive symptoms as well as cognitive deficits of varying intensity.

Although antipsychotic medication rapidly reduces the frequency and severity of hallucinations in the majority of patients (7), AVHs are refractory to traditional antipsychotic drugs in 25–30% of cases (4). Psychosocial treatments, including cognitive behavioral therapy, are often applied as an augmentation to pharmacological treatment, helping to reduce the emotional distress associated with AVHs and aiming at developing new coping strategies (7). However, they rarely change the frequency of hallucinations and moreover, many patients do not manage to engage in therapy (4). Another neuromodulatory method, electroconvulsive therapy (ECT), failed to show a specific reduction in hallucination severity (7). In a similar vein, the effectiveness of repetitive transcranial magnetic stimulation (rTMS) is still highly controversial (8–10). Consequently, AVHs remain one of the central targets in treatment of schizophrenia, including experimental therapies [e.g., Ref. (11)].

Neurofeedback (NF) based on real-time functional magnetic resonance imaging (rt-fMRI) is a newly emerging technique with high potential for clinical applications in psychiatric disorders (12, 13). It allows subjects to voluntarily change the activity in a selected brain region [for a review, see Ref. (14, 15)] and elicit behavioral changes [for a review, see Ref. (16)]. In the first study applying fMRI-based NF in schizophrenia, nine patients learned to regulate their hemodynamic response in bilateral anterior insula (17). The training improved patients' abilities to recognize disgust faces, but they were less accurate in recognition of happy faces. Although the study did not focus on clinical improvement, it showed patients' ability to learn volitional brain control using rt-fMRI. A clinical improvement in positive and negative symptoms of schizophrenia was demonstrated in electroencephalography (EEG)-guided NF, with its effects evoking long-lasting results confirmed in a 2-year follow-up (18). fMRI-based NF has the potential for higher specificity and has been suggested as experimental treatment for AVH in addition to and in combination with its EEG-based counterpart (11).

To determine the underlying pathophysiology, neuroimaging studies on AVHs in schizophrenia have been carried out for over 25 years, demonstrating an involvement of a wide network of brain areas including secondary (and occasionally primary) sensory cortices, prefrontal and premotor cortex, anterior cingulate cortex (ACC), as well as subcortical and cerebellar regions [for a review, see Ref. (3, 19)]. Among them, the ACC has a key role in regulating emotions, goal-directed behaviors, attentional processes, response selection, online source monitoring, and cognitive control (20, 21). Moreover, the ACC is involved in differentiating between self- and not self-related stimuli (22), placing it as a good candidate to differentiate between inner speech and external stimulation. Furthermore, a recent meta-analysis on AVHs demonstrated decreased ACC activity in hallucinating as compared to non-hallucinating schizophrenia patients and healthy subjects (23). Although other brain regions, such as the superior temporal gyrus [STG (24, 25)] or the inferior frontal gyrus [Broca's area (24)], may be equally important in psychopathology of AVH, we chose ACC as a target region for our study. First, the ACC has shown feasibility for NF studies in healthy subjects (26–31) and even in patients with schizophrenia (32, 33). Second, our research group has expertise in fMRI NF of this region, e.g., the successful upregulation of the rostral ACC was associated with increase in positive affect (27, 31) and improvement of emotional perception of voices (27).

Within the current study, we aimed to explore feasibility and the variability of effects of ACC regulation on AVHs. Therefore,

three patients with schizophrenia, suffering from treatment-resistant AVHs, learned voluntary control over ACC activity using fMRI-based NF. We expected that successful upregulation will lead to a decrease in severity of AVHs, to improvement of psychopathology, particularly concerning positive symptoms, and to an increased valence of the perceived voices [in accordance with Ref. (27)].

MATERIALS AND METHODS

Participants

Three right-handed patients with schizophrenia who suffered from different types of treatment-resistant AVHs participated as pilot subjects in the study. All three patients were diagnosed with schizophrenia according to the Structured Clinical Interview for DSM-IV-axis I disorders [SCID-I (34)]. They did not exhibit current psychiatric or neurological comorbidities. Severity of positive and negative symptomatology, as well as general psychopathology, was assessed by the Positive and Negative Syndrome Scale [PANSS (35)]. In order to assess the effect of NF training on AVHs and affect, directly before and after the measurement on each day, we examined severity of the AVHs using the Auditory Vocal Hallucination Rating Scale [AVHRS (36)], while current affective state was assessed with the PANAS (37). Additionally, patients were interviewed about the strategies used for regulation. After the measurement on each training day, they were asked to specify on a 10-point scale the degree of subjectively perceived control over their ACC activity (0 = no control at all and 10 = absolute control).

The patients were naïve to NF. Written informed consent was obtained prior to participation. The study protocol was approved by the Ethics Committee of the Medical Faculty of the RWTH Aachen University, Germany, in accordance to the Declaration of Helsinki.

Patient 1

Patient Demographics

The first patient was a 49-year-old woman. She had a polytechnic degree but was receiving early retirement pension. She had no partner.

Symptomatology

The patient was diagnosed with schizophrenia of the undifferentiated subtype. Schizophrenia was first diagnosed 15 years ago, and she was continuously hearing voices since that time. Periodically, she also experienced tactile as well as olfactory hallucinations. She currently showed a mild form of paranoia (e.g., people talking about her). Over the years, she progressively developed a negative symptomatology with blunted affect, poverty of speech, and slight difficulties with abstract thinking (see **Table 1**). At the time point of the study, patient 1 was medicated with clozapine (450 mg/day), aripiprazole (22.5 mg/day), and citalopram (30 mg/day) on a stable dose for 5 months.

Characteristics of Auditory Hallucinations (According to AVHRS)

Patient 1 was continuously hearing several voices simultaneously, often more than 10 different ones speaking at once. The voices were mostly commenting her behavior, affronting her, or devaluing her, but there were also positive voices encouraging her. The patient perceived to have no control at all over the voices and felt moderately disturbed by them.

Patient 2

Patient Characteristics

The second patient was a 33-year-old married woman with a university degree in sport sciences. At the time of the study, she was an occupational therapist working with children.

Symptomatology

The patient was diagnosed with a schizophrenic disorder, not otherwise specified. She had been hearing voices for 1½ years. In addition to auditory hallucinations, she sometimes experienced olfactory hallucinations such as smelling smoke. Further, she reported a lifetime diagnosis of posttraumatic stress disorder (PTSD) and one episode of a major depression. At inclusion, she demonstrated symptoms neither of depression nor of PTSD. Positive symptomatology was moderate and negative symptoms were absent. The patient was not medicated at the time of the study (see **Table 1**).

Characteristics of Auditory Hallucinations (According to AVHRS)

At the moment of the study, the patient heard six voices that commented her behavior. She heard the voices at least every hour and reported to sometimes have control over them. She reported that at times, she was able to voluntarily induce pleasant voices by imagining activities she likes. Further, she described that she could sometimes stop the voices by "telling them insistently to shut up" or by concentrating on something else.

Patient 3

Patient Characteristics

The third patient was a young man of 24 years, with a high-school degree. He was doing part-time jobs once in a while and had no partner. He was smoking about one package of

TABLE 1 | Demographic and psychopathological information of the patients.

	Gender	Age	Education (years)	Diagnosis (ICD-10)	Duration AVHs (years)	PANSS pos.	PANSS neg.	PANSS pp.	Medication
Patient 1	Female	49	18	F20.34	15	12	18	32	Yes
Patient 2	Female	33	18	F20.94	1.5	19	7	26	No
Patient 3	Male	24	10	F20.04	4	18	20	31	Yes

PANSS pos, PANSS positive score; PANSS neg, PANSS negative score; PANSS pp, PANSS general psychopathology score.

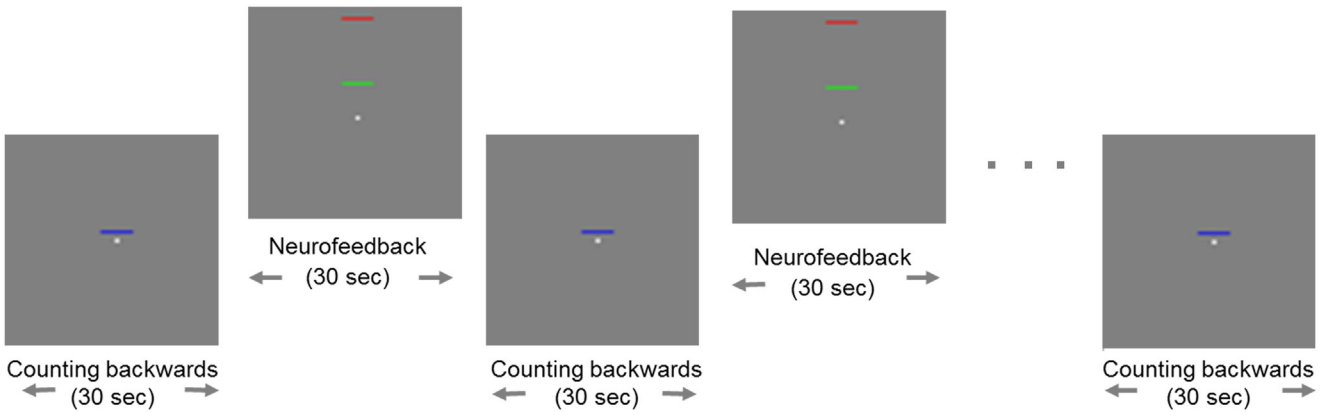

FIGURE 1 | **Example of a neurofeedback run**. Blocks of regulation alternated with blocks of baseline ("counting"). During regulation blocks, the fixed red bar in the upper part of the screen served as a marker of the highest ACC activity as a target. The green moving bar indicated the current level of activity in the ACC, which should be moved toward the red bar. The baseline block was indicated by a static blue bar in the center of the screen.

cigarettes per day for the last 5 years. On the third day of the NF training, the patient stopped the measurement during the third NF run because he suddenly became frightened in the MR scanner. He heard a voice telling him to stop. Therefore, on the third day, we obtained data from only two NF runs and no posttest.

Symptomatology

Patient 3 had a diagnosis of schizophrenia of the paranoid-hallucinatory subtype. After consuming amphetamines at a party 4 years before the study, he has continuously heard voices. He had five hospitalizations since then. During adolescence, he consumed a variety of drugs, but mainly cannabis and amphetamines. During acute phases of the illness, he experienced visual hallucinations and strong paranoia as well. At inclusion, he was hospitalized and exhibited moderate positive and negative symptomatology (see **Table 1**). He was medicated with clozapine (400 mg) for almost 2 years. The dose had not been changed over the last 6 months.

Characteristics of Auditory Hallucinations (According to AVHRS)

The patient heard five different voices that were threatening him. He perceived the voices as ghosts, which were talking about death and giving him orders. The patient felt very disturbed by the voices and indicated strong suffering. He reported to have no control at all over the voices.

Experimental Stimuli and Task

All participants were trained to control activity in the ACC by means of rt-fMRI on three separate days within 1 week. On each day, they performed three NF training sessions, each consisting of eight regulation blocks and nine baseline blocks (30 s each; see exemplary run in **Figure 1**).

Change of activity in the ACC was indicated by a green bar moving up- or downwards, while a fixed blue bar indicated the baseline condition [see also Ref. (27)]. A fixed red bar in the regulation condition served as a regulation target. It indicated the upper limit of ACC upregulation. Subjects were instructed to raise the green bar in direction of the red bar using different mental strategies. During the baseline blocks, participants' instruction was to count backwards from 100. The feedback was updated every repetition time (TR; 1 s).

Before the actual NF training, all subjects participated in a standardized training of mental strategies for ACC self-control. They received standardized instructions to recall positive emotional autobiographical memories, to imagine performing their hobby (such as engaging in sportive or musical exercise), or to concentrate on a specific perception (such as the temperature in one of their feet) in order to increase the activity in the region of interest (ROI). These strategies already proved effective in facilitating the NF training in previous studies [e.g., Ref. (32)]. The NF procedure was explained to subjects, including the delay of the NF signal for 3–5 s due to the hemodynamic response and data processing (<1 s).

Identical pre- and posttests assessed a possible transfer of the learned regulation. During these tests, subjects were asked to regulate their ACC activity with no feedback provided. The stimulus from the regulation training (i.e., the green bar) was presented during this transfer task in a fixed position. The baseline stimulus (blue bar) indicated the counting-backwards task. In the pre- and the posttest, there were four blocks of regulation and five blocks of baseline each. The posttest also included a cognitive visuospatial interference task, an adapted version of the Simon task, to test for generalization of the NF training to a behavioral task. However, single subject analysis of these cognitive interference data were not expected to yield results and were therefore not analyzed. The task for pre- and posttest was programed with Presentation software (Version 16.3).[1]

[1] www.neurobs.com

Data Acquisition and Analyses

Functional magnetic resonance imaging was conducted using a 3-T whole body scanner (Magnetom TRIO, Siemens, Erlangen, Germany). We used a 12-channel array coil for the measurements. Sixteen transverse slices parallel to anterior commissure–posterior commissure (AC–PC) line were acquired with echo planar imaging (EPI) at a TR of 1 s (echo time TE = 28 ms; 64 × 64 matrix with 3 mm × 3 mm resolution; 3-mm slice thickness plus 0.75-mm gap). We obtained 520 volumes for each NF run (about 8.5 min) and 760 volumes for the pre- and posttest (12.5 min). A custom anatomical template mask of the ACC defined our ROI [for details, see Ref. (30)]. This ACC mask was taken as a part of the cingulate cortex as defined in the WFU Pickatlas Toolbox (38) and delineated by MNI coordinates anterior to $y = 0$ and superior to $z = 0$, yielding a volume of 15.1 ml.

The feedback signal was averaged across the ACC mask for each volume, calculated as percentage of signal change relative to the preceding baseline block and scaled that 1% represented the full regulation width. Online processing was conducted using a custom toolbox based on standard SPM procedure (39). In short, motion correction using spline interpolation with co-registration to the preselected template was implemented. A modified Kalman filter reduced outliers and high-frequency fluctuations. Low-frequency drifts were removed with an exponential moving average algorithm to improve the signal-to-noise ratio.

Offline data analysis was performed in SPM8 (FIL).[2] The first 10 volumes of each run were excluded from the analyses accounting for T1 saturation effects. Data were realigned, normalized, and smoothed with an 8-mm Gaussian kernel. All different conditions were modeled in a block design applying a generic hemodynamic response function. Within a general linear model, T-maps for contrasts of interest (*regulation versus counting*, *posttest versus pretest*) were computed separately for each day and corrected for multiple comparisons across the volume using family-wise error (FWE) correction at a corrected threshold of $p < 0.05$ and an extended threshold of 15 voxels.

ROI Analyses

Next to whole-brain analyses, we performed ROI analyses for the different contrasts of interest, first, in the target ROI, i.e., the ACC. Second, activations within the reward system measured reinforcement by the NF. These ROI masks were generated from the WFU Pickatlas Toolbox (38). The mask for the ACC was as specified above, and the reward system contained the putamen, the caudate nucleus, and the globus pallidus. We determined the peaks within both ROIs on the F-maps (across all runs of all days). Activations in this peak voxel were then plotted over the different training days and for the transfer conditions.

[2]http://www.fil.ion.ucl.ac.uk/spm/

RESULTS

Behavioral Outcomes

Patient 1

Debriefing of Applied Strategies and Subjective Feeling of Control During NF

On the first day, patient 1 reported the strategy of imagining she was cycling. Additionally, she asked one of her favorite positive voices for help. On the subsequent days, she mainly used the strategy of concentrating on her positive voice and was not able to find an alternative strategy. Subjective feelings of control over ACC activity was high on the first day and decreased subsequently (see **Figure 2**).

Changes in AVHRS Scores

After the first training day, negative voices were perceived as less intense. She was better able to ignore them, felt less disturbed by them, and suffered less. After the subsequent two training days, she reported a decrease in disturbance by and suffering from voices. However, she felt more restricted in her concentration due to the voices (see **Table 2**).

Changes in PANAS Scores

During each training day, positive mood indicators increased. Negative mood also increased on the first day and remained constant on days 2 and 3 (see **Figure 3**).

Patient 2

Debriefing of Applied Strategies and Subjective Feeling of Control during NF

On the first day, the patient imagined pleasant activities she did as a child, e.g., jumping into puddles and eating ice cream. On the subsequent days, she shifted her strategy and tried to concentrate on positive childish voices. On day 3, she imagined playing the guitar. Over all 3 days, she perceived to have control over her brain activity. The patient afterward stated that she applied similar strategies during daily life to induce pleasant voices as well. The score of subjective control over ACC activity increased slightly from day 1 to day 2 and decreased again on day 3 (see **Figure 2**).

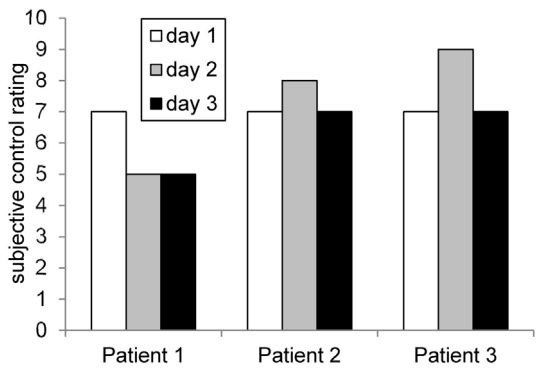

FIGURE 2 | Rating of subjective control over feedback signal across days. The profiles matched roughly the achieved ACC regulation (compare **Figure 6**).

TABLE 2 | AVHRS before and after neurofeedback training on days 1, 2, and 3 (improvements in bold).

Patient	Number of voices		Valence of voices[a]		Suffering from voices[b]		Disturbance by voices[b]		Control over voices[b]		Fear of voices[b]		Disturbed concentration by voices[b]	
Day 1														
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	5	5	**4**	**5**	**2**	**1**	**5**	**1**	5	5	0	0	1	2
2	**3**	**2**	**5**	**8**	**2**	**0**	**1**	**0**	4	0	0	0	0	0
3	1	1	**1**	**5**	**8**	**3**	**8**	**3**	2	2	0	0	**8**	**5**
Day 2														
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	5	5	5	5	**3**	**0**	**2**	**0**	**3**	**5**	0	0	2	3
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	**4**	**1**	5	5	**5**	**2**	**5**	**2**	2	2	0	0	**8**	**3**
Day 3														
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3	5	5	5	**3**	**2**	**5**	**2**	5	5	2	2	**5**	**2**
2	**2**	**0**	**5**	**0**	0	0	0	0	2	0	0	0	0	0
3	1	2	5	5	2	2	2	2	2	2	1	1	**7**	**3**

[a]*Bipolar valence scale: 0 = very negative, 5 = neutral, and 10 = very positive.*
[b]*Unipolar 10-point scale: 0 = not at all and 10 = very much.*

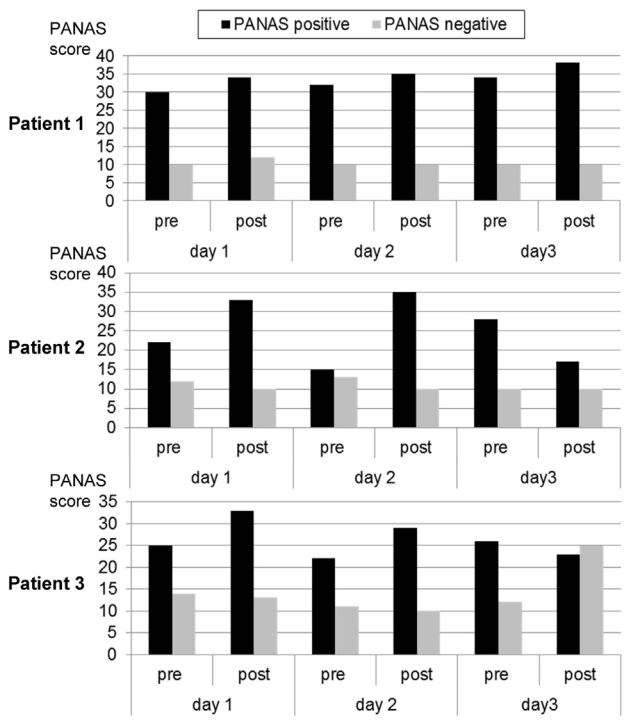

FIGURE 3 | Mood ratings according to the Positive and Negative Affect Scale (PANAS) before and after each neurofeedback training. Patient 1 exhibited a trend for continuously improved positive affect. This was similar in the other two participants, except that the third day was associated with reduced positive or increased negative affect.

Changes in AVHRS Scores

On the first day, she mainly reported a decrease in the perceived negativity of voices and small changes in suffering from voices and disturbance by voices. On the second day, there was no perceived change with respect to the voices, and on the third day, she reported an increase in perceived negativity of voices and a decrease of perceived control but also a decrease in the number of voices (see **Table 2**).

Changes in PANAS Scores

Over the first two training days, the patient reported an increase in positive mood and a reduction in negative mood. On the third day, she experienced a decrease in positive mood (see **Figure 3**).

Patient 3

Debriefing of Applied Strategies and Subjective Feeling of Control during NF

On the first training day, patient 3 reported imagining eating his favorite dish, thinking of holidays, meeting friends, or imagining his hand growing. On subsequent days, he repeated the same strategies and added imagining the exact appearance of his mother and friends as well as imagining the happiness when being discharged from the clinic. The subjective feeling of control over ACC activity increased from day 1 to day 2. On the third day, the control score decreased again (**Figure 2**).

Changes in AVHRS Scores

On the first and second days, he had the subjective feeling of a reduction of the presence and negativity of the voices during and shortly after the training. He also reported a decrease of suffering and disturbance by voices (by 5 points, respectively, on a 10-point scale) as well as a decrease in disturbances of concentration by voices. Additionally, he indicated a decrease in the number of voices heard (see **Table 2** for exact scores).

Changes in PANAS Scores

On the first 2 days, the patient reported an increase in positive mood over the course of the training. Also, his negative mood decreased. After the break-up at the third day, he reported a decrease in positive mood and a strong increase in negative mood (see **Figure 3**).

fMRI Results

Whole-Brain Analyses

Figure 4 shows an overview of whole-brain activations on the three training days in the three subjects. During regulation as compared to the counting blocks, all patients yielded significant activation clusters within the ACC as well as the reward system, visual processing areas, the precuneus, motor areas, the amygdala, and the hippocampus.

ROI Analysis – ACC

Patient 1

Within the ACC mask, significant activation emerged during the first day ($t_{peak} = 20.92$, $p_{FWE} < 0.0001$, MNI [10, 46, 6], 2474 voxels activated), during the second day ($t_{peak} = 9.69$, $p_{FWE} < 0.0001$, MNI [2, 32, 10], 1496 voxels activated), and during the third day ($t_{peak} = 11.16$, $p_{FWE} < 0.0001$, MNI [2, 34, 8], 1777 voxels activated). When directly comparing activation during self-regulation at the third and the first days, the patient did not show any significant activation at the ACC. At an exploratory uncorrected threshold of $p < 0.001$, one small cluster emerged in the subgenual ACC that was, however, not included in the ACC mask used in the training (MNI [10, 36, −10], $t_{peak} = 6.88$, $p_{uncorr.} < 0.001$, 28 voxels activated; see **Figure 5**). The overall *F*-test revealed peak ACC activation across all runs of all three training days at an anterior part of the ACC ($F_{peak} = 64.3$, $p_{FWE} < 0.0001$; MNI coordinate = [10, 46, 6]). The ACC activation at this peak voxel over the 3 days indicated successful ACC regulation on the first day and then decreasing activation over the subsequent days (see **Figure 6A**).

Within the transfer task – comparing activation at posttest with that at the pretest – patient 1 did not show any ACC activation.

Patient 2

Also in patient 2, the ACC ROI showed significant activation during the first day ($t_{peak} = 13.62$, $p_{FWE} < 0.0001$, MNI [−6, 28, 24], 2156 voxels activated), during the second day ($t_{peak} = 23.13$, $p_{FWE} < 0.0001$, MNI [−2, 14, 28], 2770 voxels activated), and during the third day ($t_{peak} = 22.01$, $p_{FWE} < 0.0001$, MNI [−2, 28, 26], 2719 voxels activated). As already indicated by the *T* values, ACC activation during the third day was significantly stronger than during the first day ($t_{peak} = 10.14$, $p_{FWE} < 0.0001$, MNI [8, 12, −8], 1482 voxels activated; see **Figure 5**). An *F*-test across all training runs revealed peak ACC activation at a relatively posterior part

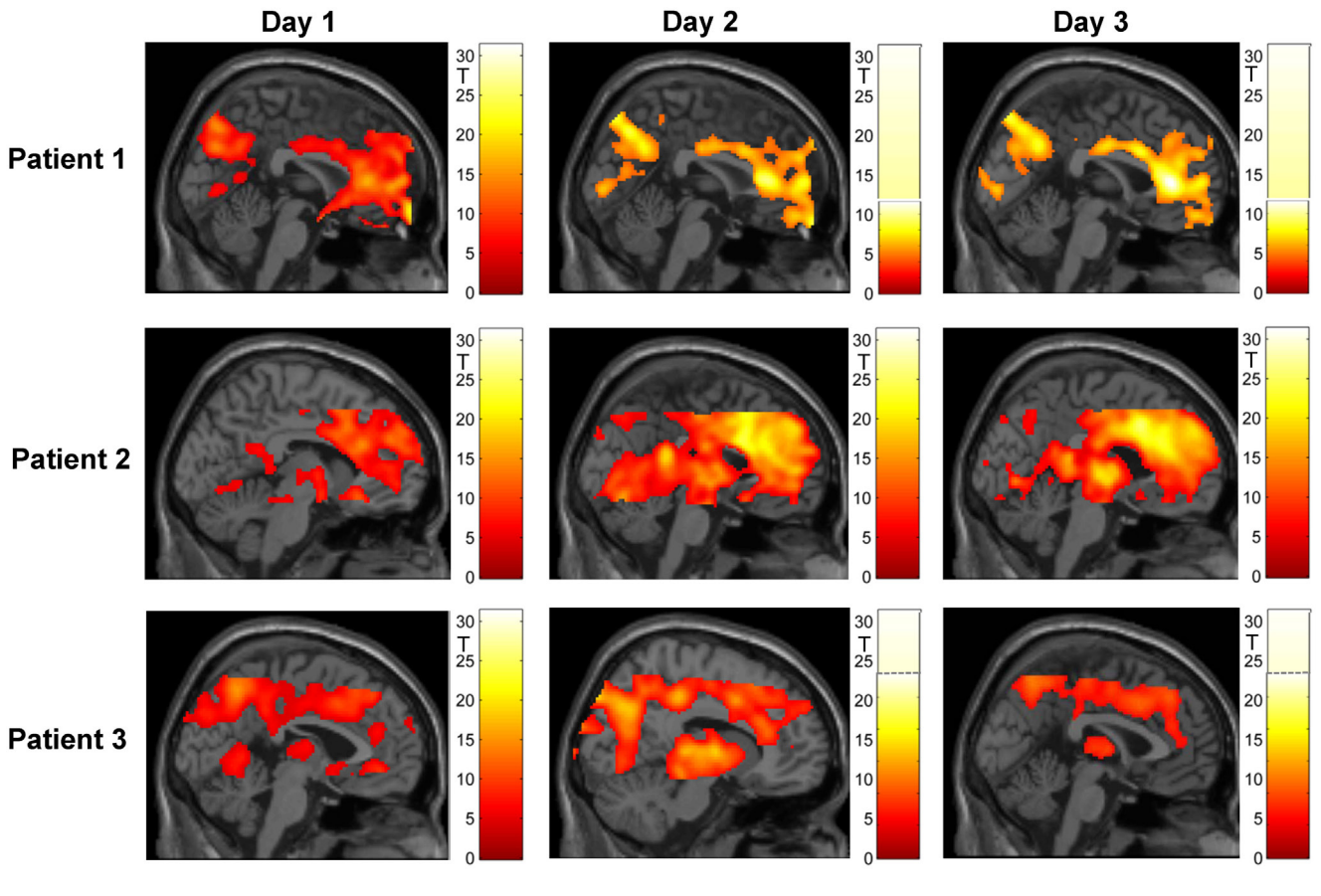

FIGURE 4 | Regulation during the neurofeedback runs as compared to baseline blocks of counting ($p < 0.05$, FWE corrected). The activation patterns did not reveal a clear increase in regulation, but the individual clusters appeared more focused on the ACC over the 3 days of neurofeedback training in patients 2 and 3. Please note that absolute *T* values differ across training days and across patients (adapted color codes). However, the identical thresholds make the cluster sizes directly comparable.

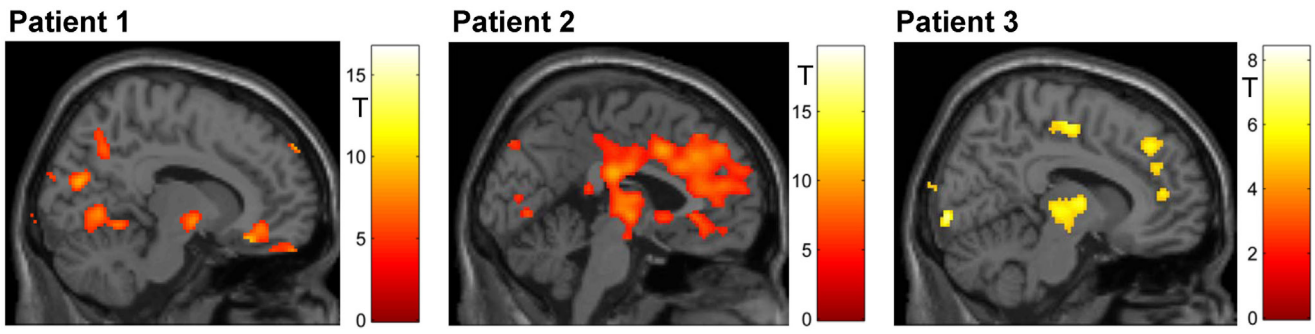

FIGURE 5 | Mapping of linear increase over days ($p < 0.05$, FWE corrected). The training led to increased activity in clusters encompassing midbrain structures (all patients) and – in patients 2 and 3 – in the ACC.

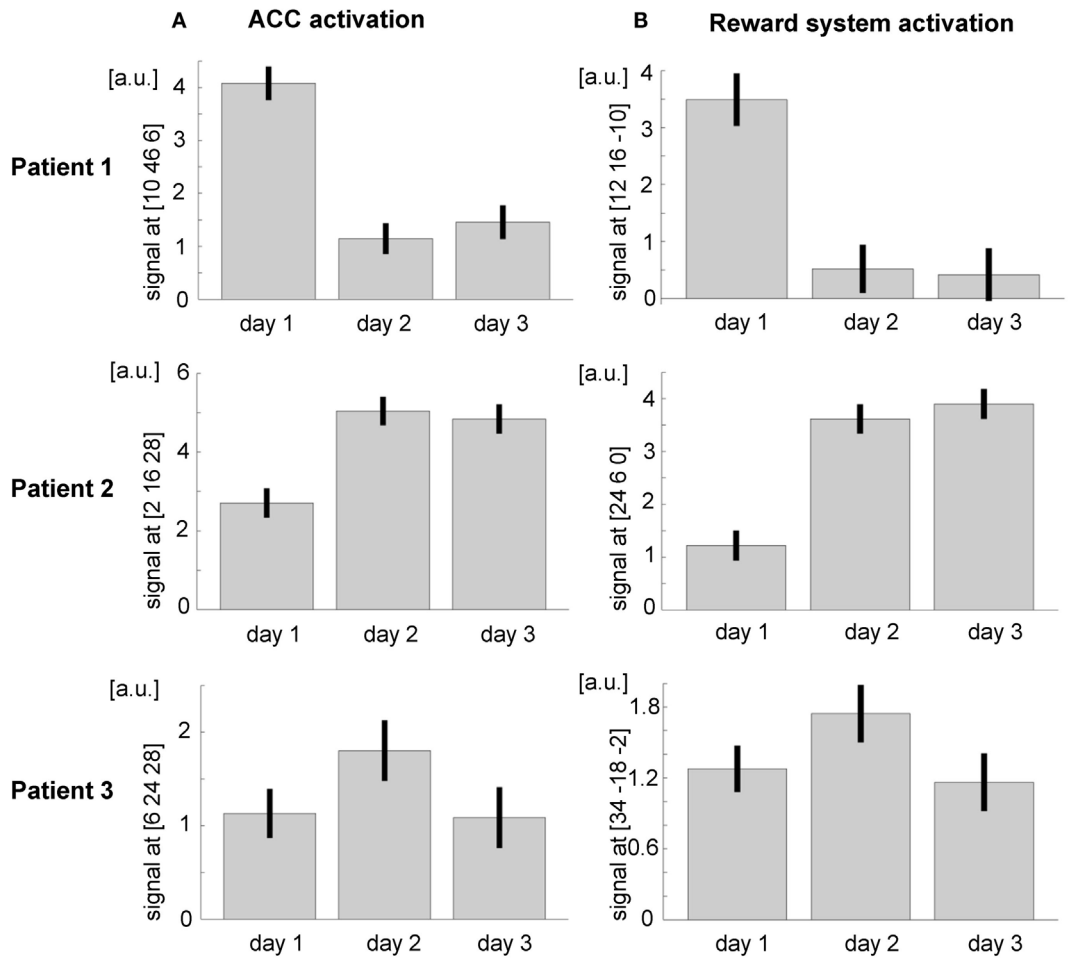

FIGURE 6 | Region of interest (ROI) analysis (A) in the ACC and (B) in the reward system revealed a general trend for increasing activity over the three training days. However, the interindividual differences are remarkable; a.u., arbitrary units.

of the ACC ($F_{peak} = 133.54.3$, $p_{FWE} < 0.0001$; MNI [2, 16, 28]). The bar plot evidences an increase of ACC activation within this peak voxel over the first two training days and constant regulation at the third training day (**Figure 6A**).

Comparing activation of the post- and the pretest within the transfer task, patient 2 showed significant ACC activation (see **Figure 7**). Bar plots indicate that during the pretest, there was no difference in peak ACC activation between regulation and

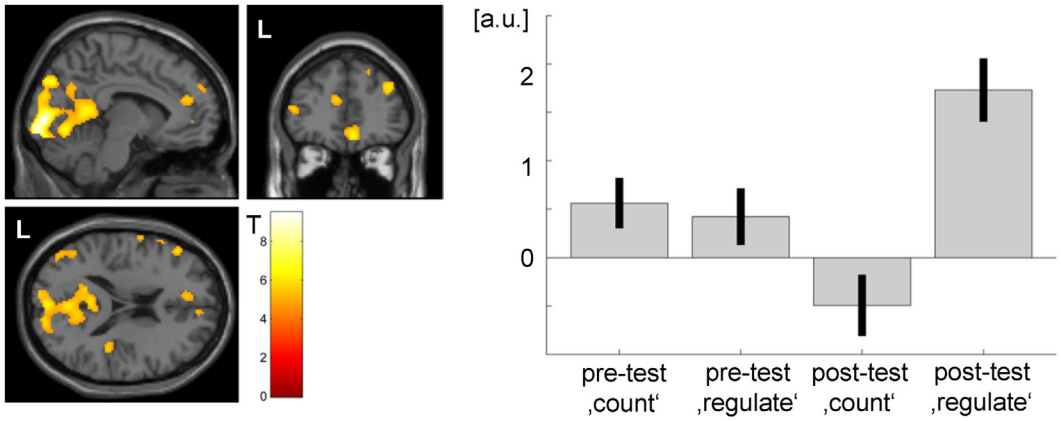

FIGURE 7 | Transfer effect in patient 2 ($p < 0.05$, FWE corrected). ACC regulation emerged also in the absence of feedback after the NF training as compared to before. However, the ACC activation cluster was noticeably smaller than during the neurofeedback training (see **Figure 3**) and did not yield significance in patient 1. The strong activation changes in the visual system may be related to attention shifts with respect to the visual task.

baseline blocks. During the posttest, there was a significant increase in peak ACC activation during the regulation phases and a slight deactivation during the baseline period.

Patient 3

Within the ACC mask, T-maps confirmed significant activation during the first day ($t_{peak} = 10.66$, $p_{FWE} < 0.0001$, MNI [−4, 42, −8], 717 voxels activated), during the second day (MNI [10, 26, 26], $t_{peak} = 9.79$, $p_{FWE} < 0.0001$, 839 voxels activated), and during the two runs completed at the third day (MNI [8, 44, 10], $t_{peak} = 6.4$, $p_{FWE} < 0.0001$, 352 voxels activated). When directly comparing ACC activation between the first two runs of the third and the first day, there was an increase of ACC activation ($t_{peak} = 5.64$, $p_{FWE} < 0.0001$, MNI [−2, 36, 28], 67 voxels activated; see **Figure 5**). The *F*-test across all training runs revealed peak ACC activation at a relatively posterior part of the ACC ($F_{peak} = 23.28.3$, $p_{FWE} < 0.0001$; MNI [6, 24, 28]). Bar plots indicate that peak voxel activation increased from the first to the second day. On day 3, decrease may be observed (see **Figure 6A**).

The third patient finished the third training day earlier, and no data of the posttest are available; thus, we could not calculate the transfer effect for this patient.

ROI Analysis – Reward System

Patient 1

The overall *F*-test shows activation in four different clusters with peak activation at the MNI coordinate [12, 16, −10]. Inspecting activation within this peak voxel over the three training days indicated reward system activation on the first day and almost no activation during the second and the third days (see **Figure 6B**). When directly comparing activation of day 3 and day 1 within the ROI mask, significant activation could only be shown in a small cluster in the left putamen (MNI [−22, 14, −10], $t_{peak} = 8.80$, $p_{FWE} < 0.0001$, 68 voxels activated; see **Figure 5B**).

Patient 2

With respect to the reward system, the *F*-test shows activation in two clusters with the peak activation at the MNI coordinate [24, 6, 0]. Activation in this peak voxel across training days showed a very similar increase as the ACC. A direct comparison of ROI activation at day 3 and day 1 indicated significant bilateral activation ($t_{peak} = 13.23$, $p_{FWE} < 0.0001$, MNI [−32, 2, −6], 3331 voxels activated; see **Figure 6B**).

Patient 3

The *F*-test shows bilateral activation with peak activation at the MNI coordinate [34, −18, −2]. Bar plots showed similar bilateral activation increases from day 1 to day 2 and a drop in activation on day 3. Comparing activations of day 2 and day 1 with T-maps indicated a significant activation increase (MNI [28, −16, 4], $t_{peak} = 6.66$, $p_{FWE} < 0.0001$, 231 voxels activated; see **Figure 6B**).

DISCUSSION

We demonstrated the feasibility of fMRI-based NF training in patients with ongoing AVHs. After the NF training, the patients reported varied degree of subjective improvement concerning disturbance through and suffering from voices, as well as decrease in their number, intensity, and negativity. In combination with previous studies employing the same paradigm, the data suggest that patients with schizophrenia can learn localized control of ACC activity as well. For the patients suffering from treatment-resistant hallucinations for years despite intensive multimodal treatment, this new approach may change their understanding of AVHs, offering subjective experience of control over the voices. Nevertheless, even those three patients exhibited remarkable individual response patterns suggesting the need for a careful patient and paradigm selection for future clinical trials. More studies are necessary to assess the clinical relevance of fMRI NF, possibly in combination with other therapeutic techniques such as cognitive behavioral therapy.

The heterogeneity between the patients was also reflected in individually differing brain networks that were activated during NF. When evaluating mood changes across the NF training, the regulation training led to increased positive

affect on the first and second days such as in a previous study with 1-day training (27). However, the participants did not profit from the prolonged three-session training. Indeed, in one subject, we even observed deterioration on the third day. Similarly, Surmeli et al. (18) demonstrated in their EEG-based NF study variability both in training duration and in clinical outcome. The authors postulate that every EEG-NF treatment protocol should be personalized to the specific patient and be regularly monitored and adjusted for an optimum treatment effect. The National Advisory Mental Health Council's Workgroup (40) urged to search for personalized therapy, based on the knowledge about the individual that differentially predicts his or her response to treatment.

Psychopathology and Neurofeedback

Personalization of treatment may be of particular interest considering the high interindividual variability between patients with schizophrenia that goes along with variability in individual activations patterns in the current study. In fact, the three patients measured in the current study showed high variability: next to differences in the exact diagnosis and duration of illness, also extrinsic factors, such as "secondary" negative symptoms, additional lifetime diagnosis of depression, and drug-related changes, may have caused further variability within the schizophrenia continuum. In accordance with the Report of the National Advisory Mental Health Council's Workgroup (40), we describe below case-oriented results in hope that they provide a more stratified approach for linking psychopathology to treatment outcome and will complement standard clinical trials.

Patient 1

Patient 1 showed successful regulation already in the first run of the first day but failed to increase the ACC activation over the course of training. The patient's symptoms were concordant with a deficit form of schizophrenia, i.e., schizophrenia with primary and enduring negative symptoms (41, 42). This patient presented a long duration of illness with symptoms being stable over time. Additionally, she was the only patient treated with a highly D2-affine antipsychotic (aripiprazole). Negative symptoms and antipsychotic medication were found to be associated with reduced reward system sensitivity (43). Indeed, this patient exhibited much lower reward system activation during NF in comparison to the other two patients. In a previous animal study, reward system involvement was confirmed an obligatory requisite for learning to control BCIs (44). Although NF strongly relies on operant conditioning (16) and, therefore, on an adequate perception of rewarding events and appropriate reactions to rewards, the patient regulated ACC activity and demonstrated a consistent clinical improvement on all training days. Moreover, her subjective feeling of control over the ACC corresponded to actual ACC activity. Because negative symptoms in schizophrenia are often associated with attention deficits, it may also have been difficult for the patient to adopt, maintain, and shift the cognitive strategies as indicated by the feedback signals. This may explain why she did not show increasing ACC activation over the training and shifted from a successful regulation strategy on day 1 to less effective strategies on the subsequent days.

Auditory verbal hallucination symptoms showed a relatively close match with the training success on the 3 days [average blood-oxygen-level dependent (BOLD) effect in ACC]. Thus, the change in the AVH symptoms may also serve as a performance indicator and probably even stronger reward than the feedback from the bar display. Hence, future studies may probe to what extent strongly anhedonic patients profit from the instruction to consider an increase of the feedback signal and additionally explore specifically strategies to modify the depicted neuronal activity based on their AVHs.

Patient 2

Patient 2 demonstrated both an increase of the ACC activation during NF from the first to the third day and a significant ACC upregulation in the transfer condition without feedback. These changes were accompanied by changes in the perception of her AVHs as well as changes in mood. While ACC activity increased on days 1 and 2 with concurrent improvements in the disturbance of AVHs, high activity on day 3 seemed to elucidate a trade-off between a decrease in the number of voices, an increase in the perceived negativity of the voices, and a decrease in mood. Insofar, the results from patient 2 do not show a clear correspondence between ACC activity and symptom experience on the third day but suggest that, at least for this patient, other brain circuitries may be required to yield constant effects on AVHs and mood. On the neuronal level, there was stronger concurrent activation of the anterior prefrontal cortex and left subgenual ACC at the first 2 days when compared to the third day. On day 3, in contrast, there was increased activation of the inferior frontal gyrus and insula. Thus, the improvement in AVH symptoms on the first days may have been due to an additional increase of prefrontal inhibition or prefrontally mediated focusing on the task (45–47). This patient might profit from feedback derived from several frontal brain areas or connectivity between the ACC and the anterior prefrontal cortex in order to achieve more stable effects of NF on symptomatology.

Importantly, after the NF training, this patient managed to upregulate her ACC even without receiving feedback. She was the only patient to show this transfer effect, which may be due to the fact that she already used similar strategies for the control of her voices before the study. If this transfer mechanism shows to be stable in the long term, it would allow voluntary control over AVHs also outside the scanner. Further, this finding would additionally strengthen long-term NF effects that may be due to neural plasticity (48). In a NF study with a small number of schizophrenia patients, Ruiz et al. (17) demonstrated this transfer effect on a trend level. In addition to increasing the number of patients, variability of patient characteristics should be considered in future studies.

Patient 3

Patient 3 increased ACC regulation over the first two training days. These neuronal changes were accompanied by mood improvements as well as relevant changes in the perception of the AVHs.

On day 3, he showed a decrease of ACC activation as well as a decrease in mood and no further perceived symptom reductions. Moreover, his subjective feeling of control over the ACC activity corresponded well with the actual ACC activity. Further, ACC activations were closely associated with the reported symptoms. However, this patient stopped the measurements on day 3 due to increased anxiety and warning of his voices. This leads to the question, if such "negative therapeutic response" (49) is an effect to consider in the NF treatment of AVHs. Indeed, many patients report AVHs as being at least in parts positive and helpful [e.g., Ref. (50)]. In combination with a growing fear to change positive aspects of the disorder, it needs to be considered whether 3 days of intensive rt-fMRI NF training within 1 week may be too exhausting for schizophrenia patients with complex symptoms. When inspecting the data, it seems that a 2-day training would have resulted in a comparable outcome. Conceivably, some patients might better profit from additional booster sessions of NF training some weeks later.

Models of Auditory Verbal Hallucinations

Several theories have been put forward to explain the occurrence of AVHs and link them to observed neuronal changes. The feed-forward model being one of the most influential [for a review, see Ref. (3, 51)]. This neurocognitive model poses that AVHs occur due to a failure to recognize self-generated inner speech (51). The aberrant corollary discharge (or efferent copy) prevents comparing information about predicted action with received sensory input (52, 53). Consequently, self-generated speech is interpreted as externally generated (3, 54–57). Corresponding to the feed-forward model, patients with AVHs show systematic biases in motor tasks and pronounced deficits in cognitive tasks assessing self-recognition (58, 59). Indeed, connectivity was disrupted between temporal and cingulate cortices in schizophrenia patients with AVH only (60), and AVHs severity correlated to functional connectivity between the ACC and the STG (61). Contrary to patients with AVH, in healthy controls and in schizophrenia patients without AVH, the connectivity between left STG and the ACC (60) or the mPFC (62) was significantly greater for other – than for self-generated speech. Conceivably, in addition to structures, such as the STG, the ACC plays a central role in symptom generation and intensity modulation of AVHs.

However, the feed-forward model fails to explain phenomenological aspects of AVHs. For instance, most hallucinations are experienced as located in external space and take the form of another person's voice, usually being experienced as "alien" (63). Cho and Wu (64, 65) pointed out that the internal articulation typically lacks properties associated with the experience of pitch and timbre distinct from one's own voice, and they propose to replace the self-monitoring theory with the concept of auditory imagery as underlying phenomenon for AVH. AVH could also be linked to an externalizing bias in reality monitoring, which results in an impaired ability to distinguish between internally generated and externally generated percepts (66). Further, Waters et al. (67) conceptualizes AVHs as memory intrusions that are not recognized as such because they lack contextual cues. Another model attributes the emergence of AVHs to the highly increased salience of internal representations in schizophrenic patients that may be mediated by abnormal dopamine levels (68, 69). Hoffman et al. (70) proposes that prepsychotic social withdrawal prompts neuroplastic reorganization by the "social brain" to produce spurious social meaning *via* hallucinations of conversational speech. This diversity of models renders it difficult to select a fitting target region for voluntary brain regulation. Although most of the fMRI studies point to STG or auditory cortices as an evident target for downregulation (24, 25), it is not clear whether these areas can be downregulated to achieve a relevant physiological effect. Further, the downregulation of a sensory area would be equivalent of directing the attention away from a sensory channel, which patients already unsuccessfully tried before. It will be interested to target those regions in future fMRI NF studies to assess their feasibility and compare with the regulation of the ACC.

Previous NF studies demonstrated that the upregulation of a single area can elicit alterations of functional and effective connectivity (48, 71). Further studies may elucidate whether the ACC upregulation also induces changes of the network dynamics. In the long term, it may be even more effective if NF would target further areas and aim at a correlated regulation. First, this would allow addressing the entire dysfunctional neuronal ensemble that predisposes AVHs (3). And second, it would enable to adjust activity of the proposed salience network that may be of importance in the change of AVHs (72, 73).

Other Neuromodulation Strategies

Despite the lack of hard evidence, EEG-based NF has been established in clinical domains such as attention deficit hyperactivity disorder (74) and epilepsy (75). For the application of EEG-based NF in schizophrenia, only case studies are available [e.g., Ref. (18)]. In general, these approaches are based on quantitative EEG, i.e., they attempt a "normalization" of oscillatory activity during resting state. This technique is widely available and relatively cost-effective. However, the training takes weeks to months [e.g., the average of 58.5 training sessions in Ref. (18)]. This is in an interesting difference to fMRI-based approaches. In our study and others [e.g., Ref. (76, 77)], successful control with fMRI-BCI tended to emerge extremely fast or even abrupt. It is unclear where this difference emerges from. Potentially, the precise localization supported by the modular organization of brain function enables a more direct control of the localized BOLD signal rather than EEG activity from distributed sources.

Alternatively, external neuromodulation strategies are available. In AVHs, particularly TMS has been applied. Typically, using repetitive stimulation to reduce local brain activity, rTMS studies targeted left temporoparietal cortex (10). Nevertheless, treatment success has been mixed, and improvements, such as localization based on fMRI activation maps, have been suggested (78). Moreover, TMS is limited to targets close to the surface; therefore, fMRI-based NF is ideally suited to base the target ROIs on such navigator [compare Ref. (79) for this strategy in depression]. The current study applied a predefined ROI of (parts of) the ACC. This region could not be addressed by TMS due to its anatomical localization. Indeed, such extended regions would not be assessable even to deep brain stimulation [DBS; see Ref. (80) for application in depression]. Finally, transcranial direct current stimulation (tDCS) is rather limited in targeting specific

anatomical structures and to our knowledge has not been applied in AVHs yet. The combination of different neuromodulation strategies seems promising to optimize modulation strength, localization, and long-term effects, e.g., a combination of TMS and EEG-NF showed promising effects in autism (81). Such strategies could encompass TMS to localize the optimal modulation location, fMRI-NF to achieve rapidly a regulation strategy, and EEG-NF to maintain the learning effect over long term.

Limitations

The most prominent limitation of the study is the small number of patients that does not allow for generalizing the findings to populations. However, the study is not aimed at demonstrating effectivity of the NF treatment or even making treatment suggestions. No systematic catamnesis was assessed because we did not expect persistent clinical affects from the one-time NF intervention. The study only provides evidence for the feasibility of ACC NF in patients with ongoing AVHs. The observed variability of clinical findings and the approaches to the feedback training offers information for the design of systematic studies, in particular clinical trials. It seems relevant to consider factors interfering with reward processing such as anhedonia and antipsychotic medication. Conceivably, the drug treatment alters the neuroplasticity or the ability to learn NF. Indeed, such a group of treated patients showed a different pattern in the learning of ACC regulation but quantitatively were as capable to learn ACC NF as matched controls (32). However, antipsychotics will be present in virtually all groups of schizophrenia patients with treatment-resistant AVHs. The effort for the patients to undergo the NF training should not be underestimated as well as the mixed motivation of the patients, since there are often also positive aspects of the hallucination, which the patients may fear losing after the training. Particularly, we cannot exclude the non-specific influence of undergoing the procedure, since there was no control patient group (e.g., who learned the control of a different brain region).

Further, no formal long-term follow-up was conducted with the patients, which is underrepresented in fMRI-BCI research in general (17, 71). In informal reassessments during clinical visits, none of the patients reported adverse effects and two of the patients claimed to have different strategies in dealing with their AVHs up to few weeks after the training. However, in contacts more than a month after the study, none of the patient had the impression that there was any influence on their symptoms. Individual variability and fluctuation in the disease course may override the – so far rather small – effects of the NF training. This may change with better targeted NF protocols. However, based on the clinical impression, we would suggest that at least monthly reminder session would be advisable for clinical trials.

Finally, other neural networks may serve as target for the NF training. The current pilot study did not compare the regulation of the ACC with other regions. Thus, unspecific processes may have engaged the ACC during the regulation attempts and contributed to the observed activation pattern. In particular, performance monitoring and related psychological functions may yield baseline activation during the regulation blocks. Nevertheless, NF is thought to – at least – increase these activations [e.g. Ref. (27)]. Further, experimental trials or case studies may be directed to alternative regulation targets in AVH. In particular, the auditory cortex may be an important target for downregulation [see Ref. (81)], but so far, there is little experience in self-regulation of these areas with fMRI-NF [see review in Ref. (82)].

CONCLUSION

We explored the application of fMRI-based NF in therapy-resistant AVHs. Three patients suffering from AVHs due to schizophrenia trained the self-regulation of ACC activity. In general, they achieved control of areas encompassing the ACC, and in one patient, the transfer of regulation to a condition without NF could be shown. Further regulation success was associated with changes in symptom scores. However, variability of disease presentation and antipsychotic medication was reflected in the individual repose patterns. These data should inform future NF studies in AVHs; among others, such trials need to take into account individual differences in reward processing, fatigue, and motivation.

AUTHOR CONTRIBUTIONS

Idea and preparation: MD, KAM, YK, MZ, SS, and KM; clinical examination: MD, EA, and AG; data evaluation and interpretation: MD, KAM, PS, SB, and KM; manuscript writing: MD, KAM, SB, PS, and KM; and manuscript editing: all.

FUNDING

This research project was supported by the German Research Foundation (DFG; MA 2631/6-1, BE 5328/2-1), the Federal Ministry of Education and Research (APIC: 01EE1405B, 01EE1405C), the Brain & Behavior Research Foundation, and the START program of the Faculty of Medicine, RWTH Aachen. KAM was supported by a habilitation grant (Habilitationsstipendium) of the Faculty of Medicine, RWTH Aachen.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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METHODS
published: 27 June 2016
doi: 10.3389/fpsyt.2016.00103

Translating Neurocognitive Models of Auditory-Verbal Hallucinations into Therapy: Using Real-time fMRI-Neurofeedback to Treat Voices

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Auditory-verbal hallucinations (AVHs) are frequent and disabling symptoms, which can be refractory to conventional psychopharmacological treatment in more than 25% of the cases. Recent advances in brain imaging allow for a better understanding of the neural underpinnings of AVHs. These findings strengthened transdiagnostic neurocognitive models that characterize these frequent and disabling experiences. At the same time, technical improvements in real-time functional magnetic resonance imaging (fMRI) enabled the development of innovative and non-invasive methods with the potential to relieve psychiatric symptoms, such as fMRI-based neurofeedback (fMRI-NF). During fMRI-NF, brain activity is measured and fed back in real time to the participant in order to help subjects to progressively achieve voluntary control over their own neural activity. Precisely defining the target brain area/network(s) appears critical in fMRI-NF protocols. After reviewing the available neurocognitive models for AVHs, we elaborate on how recent findings in the field may help to develop strong *a priori* strategies for fMRI-NF target localization. The first approach relies on imaging-based "trait markers" (i.e., persistent traits or vulnerability markers that can also be detected in the presymptomatic and remitted phases of AVHs). The goal of such strategies is to target areas that show aberrant activations during AVHs or are known to be involved in compensatory activation (or resilience processes). Brain regions, from which the NF signal is derived, can be based on structural MRI and neurocognitive knowledge, or functional MRI information collected during specific cognitive tasks. Because hallucinations are acute and intrusive symptoms, a second strategy focuses more on "state markers." In this case, the signal of interest relies on fMRI capture of the neural networks exhibiting increased activity during AVHs occurrences, by means of multivariate pattern recognition methods. The fine-grained activity patterns concomitant to hallucinations can then be fed back to the patients for therapeutic purpose. Considering the potential cost necessary to implement fMRI-NF, proof-of-concept studies are urgently required to define the optimal strategy for application in patients with AVHs. This technique has the potential to establish a new brain imaging-guided psychotherapy for patients that do not respond to conventional treatments and take functional neuroimaging to therapeutic applications.

Keywords: hallucinations, neurofeedback, fMRI, therapeutic strategies, anterior cingulate cortex

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Matthias Kirschner, Zurich University Hospital for Psychiatry, Switzerland
Laura Diaz Hernandez, University of Bern, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *15 January 2016*
Accepted: *31 May 2016*
Published: *27 June 2016*

Citation:
Fovet T, Orlov N, Dyck M, Allen P, Mathiak K and Jardri R (2016) Translating Neurocognitive Models of Auditory-Verbal Hallucinations into Therapy: Using Real-time fMRI-Neurofeedback to Treat Voices. Front. Psychiatry 7:103. doi: 10.3389/fpsyt.2016.00103

INTRODUCTION

Auditory-verbal hallucinations (AVHs), i.e., hearing voices in the absence of appropriate external stimuli, are frequent experiences in schizophrenia, with a lifetime prevalence of 60–80% (1, 2). AVHs are often strongly disabling symptoms, which can be refractory to conventional psychopharmacological treatment in more than 25% of the cases (3). A recent meta-analysis supports the effectiveness of cognitive–behavioral therapy (CBT) in the treatment of AVHs (4). However, in the specific case of treatment-refractory symptoms, CBT seems to have modest and only short-term benefits (5, 6).

In recent years, the number of brain imaging studies in the field of AVHs has grown substantially, leading to a better understanding of this subjective phenomenon (7, 8). Recent progress in deciphering the neural underpinnings of AVHs has strengthened transdiagnostic neurocognitive models that characterize AVHs, but, more specifically, these findings built the bases for new therapeutic strategies. Indeed, brain imaging now allows for the identification of therapeutic targets by determining the brain regions involved in the occurrence of AVHs. For example, based on findings implicating the left temporoparietal cortex in AVHs, *repetitive Transcranial Magnetic Stimulation* (rTMS), a non-invasive brain stimulation method, has been used to target this region and shown to have a significant, although moderate, effect in alleviating drug-resistant AVHs (9).

Recently, technical improvements in real-time functional magnetic resonance imaging (fMRI) have enabled the development of fMRI-based neurofeedback (fMRI-NF) (10). During fMRI-NF, brain activity is measured in real time and fed back to the participant, usually using visual or auditory information, in order to facilitate voluntary control over the participant's own neural activity. Considering the advances in the identification of anatomical and functional changes linked with AVHs, fMRI-NF strategies constitute a promising tool, giving the possibility for patients to normalize their brain activity level or connectivity strength in the AVHs-specific brain regions, and thus reduce symptom severity. Precisely defining the target brain area/network(s) appears crucial for future fMRI-NF protocols designed to treat AVHs.

After briefly reviewing current literature about the neural basis of AVHs (mainly neurocognitive models and brain imaging findings) and providing an overview of how fMRI-NF can be used in psychiatry, the review will then elaborate on how recent advances in the field may help to develop strong *a priori* strategies for fMRI-NF target localization. Three different fMRI-NF strategies dedicated to AVHs' treatment will be proposed. Current limits, potential difficulties for patients with schizophrenia to benefit from fMRI-NF, as well as future directions will be critically discussed.

WHAT IS fMRI-NEUROFEEDBACK?

fMRI-Neurofeedback: Principles

Neurofeedback is a non-invasive technique enabling participants to achieve voluntary control over the neuronal activity of one or more brain regions [for a recent review on the technique, see Ref. (11)]. In the case of fMRI-NF, this is accomplished by deriving and presenting blood oxygen level-dependent (BOLD) signal derived from the target brain area(s) to the subject in real time (12). Visual feedback is primarily used, but neurofeedback derived from other or combination of different modalities is also possible. Visual feedback can be presented in various formats: from a thermometer display to more complex interfaces [e.g., social feedback Ref. (13)]. The participants use this feedback to self-regulate their neuronal response or adjust their cognitive strategy, during the experimental task in real time (see **Figure 1A**). They must be informed in detail(s) of the hemodynamic delay of 4 or 5 s (due to the BOLD response) to update the neurofeedback signal. The general experimental design of an fMRI-NF protocol is described in **Figure 1B**. This technique is currently being used in cognitive modification (14) and clinical trials (15).

fMRI-Neurofeedback in Psychiatry

fMRI-based neurofeedback could be a useful tool in psychiatry. Numerous studies have shown the benefits of fMRI-NF to relieve non-psychiatric clinical symptoms. Haller et al. demonstrated therapeutic effects of fMRI-NF (focusing on downregulation of auditory cortex) in the treatment of chronic tinnitus (16). deCharms et al. also published promising results for the management of chronic pain (17), although these results failed to be replicated (12).

Furthermore, recent progress in the field of brain imaging has allowed the identification of functional changes associated with a range of psychiatric symptoms (18). Because fMRI-NF can potentially be used to normalize the activity level of specific brain regions (which should be a key issue in new treatments), fMRI-NF could offer a new interesting way to treat mental health symptoms (19). To date, promising positive results have been already demonstrated in major depressive disorder (15, 20) and addiction (21–23).

Why Using fMRI-Neurofeedback for Auditory-Verbal Hallucinations in Schizophrenia?

In a paper published in 2012, McCarthy-Jones stressed the potential interests of developing neurofeedback as a new treatment of AVHs (24). In the past decade, significant progress in identifying the neural underpinning of AVHs has been made. This knowledge can inform on a target region for fMRI-NF.

To date, only a few studies reporting the use of neurofeedback in patients with schizophrenia have been published. Most of these studies used electroencephalogram (EEG)-based neurofeedback (the principle is the same as fMRI-NF, but the brain activity is measured with EEG) [e.g., Ref. (25–27), with one current study running a trial for the treatment of AVHs (28)]. Two studies have used fMRI-NF in patients with schizophrenia. Ruiz et al. demonstrated that patients with schizophrenia ($n = 9$) were able to achieve voluntary control of bilateral anterior insula cortex using an fMRI-NF protocol (29). Participants completed four training sessions spread over 2 weeks. Each training session comprised three runs of self-regulation training. Each run consisted of six

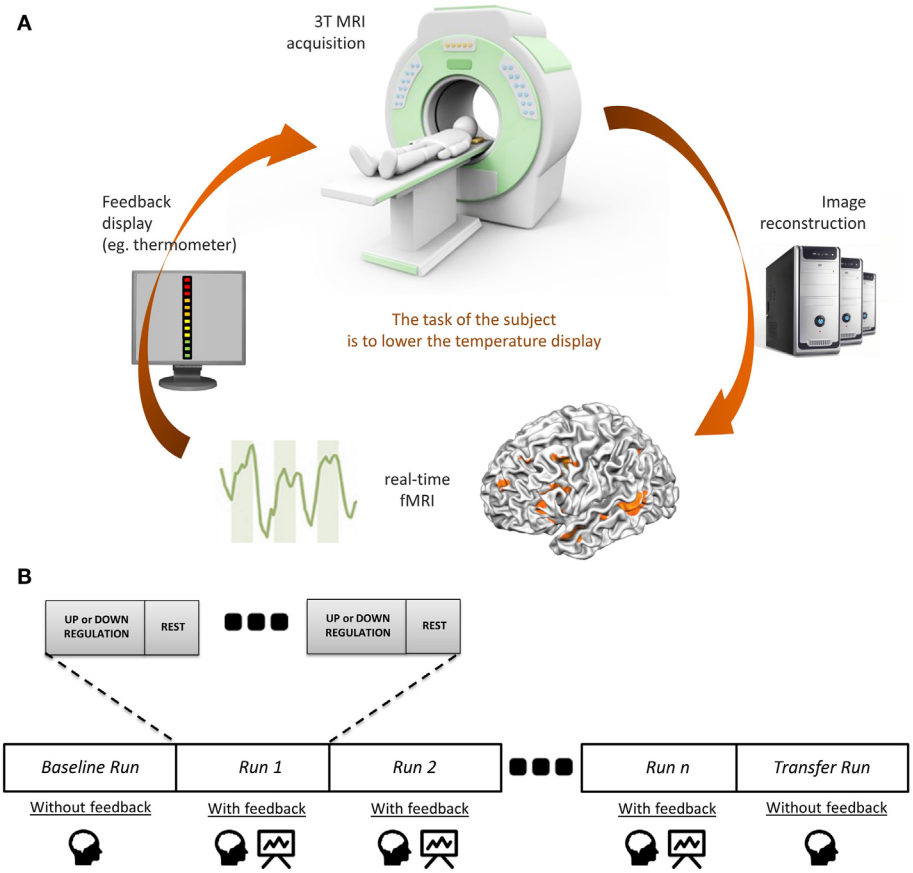

FIGURE 1 | **The principles of fMRI-neurofeedback**. **(A)** Diagram of an fMRI-based neurofeedback system. **(B)** The neurofeedback training in fMRI-neurofeedback protocols.

upregulation and seven baseline blocks (30 s blocks). Patients were instructed that the recall of emotionally relevant past experiences combined with the feedback could enable them to control the thermometer bars. No specific emotional cues or recall strategies were given. The gain in the voluntary control was associated with behavioral changes assessed on a facial emotion recognition task (i.e., patients recognized disgust faces more accurately and happy faces less accurately after the fMRI-NF training). Furthermore, the training was associated with an increase in the number of the incoming and outgoing effective connections in the anterior insula. This proof-of-concept study demonstrates that patients with schizophrenia can not only benefit from fMRI-NF and learn volitional brain regulation but also find that such learning is accompanied with behavioral changes and neurophysiological changes in the underlying brain network (29). More recently, Cordes et al. showed that patients with schizophrenia ($n = 11$) were also able to learn to control the activity of their anterior cingulate cortex (ACC) (30). Here, three fMRI-NF training sessions were completed in 1 week. Each session included three runs consisting of eight regulation and nine baseline blocks lasting 30 s each. During the fMRI-NF session, the participants were asked to upregulate the signal using individual mental strategies. However, some template strategies from different cognitive domains were given: positive autobiographic memories, picturing oneself doing sports or playing an instrument, and concentration on given perceptions like feeling the temperature of one's own left foot. The results demonstrated that both patients with schizophrenia and healthy controls were able to develop control abilities. However, they used different neural strategies: patients activated more of the dorsal and healthy controls activated more of the rostral subdivision of ACC. They also used different mental strategies: patients mainly imagined of music, whereas healthy controls used more imagined sports.

In summary, evidence suggests that patients with schizophrenia are able to learn voluntary control over their brain in spite of their pathology. All of this makes the fMRI-NF a promising tool to tackle frequent and disabling symptoms in this population, such as AVHs.

WHAT DO WE KNOW ABOUT THE NEURAL BASIS OF AUDITORY-VERBAL HALLUCINATIONS?

Neurocognitive Models

Phonologically, AVHs are heterogeneous in form and content (31). They vary from acousmas (primitive sounds, such as blowing, shooting), utterances, or simple words to full conversations, with

defined characteristics such as pitch, volume, and accent. They might consist of a single voice or a collection of voices that speak the individual's thought aloud, issuing commands and instructions, or provide a running commentary on the person's behavior. The voices might be familiar or unknown (32). They often carry power, authority (33), and a negative quality [e.g., Ref. (2, 34)], and persons experiencing them often feel that they have no or little control over their AVHs (2).

From a neurocognitive perspective, hallucinations are erroneous perceptions or sensory deceptions without the presence of external stimuli and have been attributed to erroneous integration of sensory and cognitive processes (35) that may influence conscious perception (36). Brain regions that have been implicated in the experience of AVHs include the auditory cortex and the ventral attentional system that spontaneously orientates attention toward an incoming stimulus (37, 38).

A number of neurocognitive models have been proposed to account for heterogenic phenomenology of AVHs (39).[1] The current models are based on research findings that illustrate the following contributing factors to the experience of AVHs. These are AVHs have clear perceptual qualities, AVHs are internally generated but are not attributed to an internal source, those experiencing AVHs have a reduced sense of control over the onset, content, and frequency of AVHs, and AVHs often carry an emotional component.

Externalization, or lack of agency, was explained by a model proposed by Frith (40), which postulated the breakdown in a physiological process known as self-monitoring. This model is based on the assumption that in patients with schizophrenia, inner speech and/thoughts fail to be recognized as self-generated due to a self-monitoring deficit; reflecting a dysfunction of the efference copy or corollary discharge mechanism that accompanies a motor action, such as speech or movement (41, 42).

In those experiencing hallucinations, the efference copy of inner speech does not produce a corollary discharge of the expected experience. Consequently, this failure in the corollary discharge mechanism can produce confusion regarding the agency between one's own thoughts and externally generated voice, potentially resulting in an external attribution of the experience and the experience of AVHs. At a neuronal level, this may result in greater activity in the auditory cortex when self-generated speech or inner speech is produced (42, 43).

At a behavioral level, it has been shown that patients with schizophrenia and AVHs exhibit difficulty in identifying self-generated information (44–46). However, models based on the misattribution of inner speech do easily account for observed phenomenology of AVH (47, 48) and there is no evidence that the cancelation or suppression of reafference indicates the source of a sensory event: zero signal is not the same as self-generation (49).

Another early model postulates a deficit in source monitoring or reality testing (50). Source monitoring is a meta-cognitive (thinking about thinking) process that enables us to make attributions as to origins of beliefs and thoughts in order to form a cohesive representation of an experience (50). Bentall et al. suggested that patients with schizophrenia have deficits in discriminating between external (real) and internal (imagined) events, accompanied with a specific externalization bias. For example, it has been demonstrated that patients with schizophrenia and AVHs were more prone to misattribute self-generated items to other sources (51). Further, the experience of AVHs has also been related to deficits in reality testing. Based on signal detection theory (SDT), it was suggested that patients with schizophrenia and AVHs show a shift in the decision criterion (the point at which a person decides they perceive a stimulus) (52). SDT proposes that detection of a stimulus is based on two premises: perceptual sensitivity – the general efficiency of the perceptual system and response bias – the subjective decision criteria to deciding that a perceived event is a stimulus. For example, patients with schizophrenia and AVHs demonstrate higher perceptual sensitivity to detecting words or sounds embedded in white noise, as compared to non-hallucinating patients, but lower sensitivity compared to healthy controls (53). Further, patients with current AVHs also demonstrate a response bias, i.e., indicated that they were certain that a stimulus was presented, even when it was absent, suggesting that the perception/signal detection is unimpaired in patients with AVHs, but there is uncertainty in the signal recognition. This uncertainty, accompanied by a misattribution bias and source/reality monitoring deficits, perpetuates the attribution of thoughts to an external source. This may result in perceptual hypervigilance (54, 55) in responding to biases and lead to (strong) consolidation of such responses with time (56).

Substantial evidence supports the link between AVH and self-, source, and reality monitoring and has been provided over the last two decades (56, 57). Nonetheless, these early models alone cannot account for the presence of AVHs, as they fail to account for certain aspects of their phenomenology. AVHs are often experienced in the second and third person, they may consist of multiple voices that are not the voice of the experiencer, and the experiencers often converse with the AVHs (45, 49).

More recently, a number of models have been developed in order to incorporate the complex phenomenology of AVHs, by integrating the available neurophysiological data and adapting the predictive processing framework (PPF). For example, Allen et al. (35) proposed a neuroanatomical model founded upon a network of brain areas involved in both cognitive and perceptual processing; suggesting that hyperactivation of perceptual regions, including the primary and secondary auditory cortices evident during AVHs (38, 49, 58, 59), and in related speech and language areas (43, 58, 60). On the other hand, Wilkinson (61), adopted the PPF [e.g., Ref. (62)] to account for the phenomenology of AVH. In the framework of PPF, neuronal systems have evolved to predict statistical regularities in the environment based on prior experiences (63). Through successfully encoding predictions in an accurate manner, they minimize prediction errors or deviations from these predictions, and these are seen as the neural systems demonstrating an attenuated response to these predictable events; permitting the serial updating of prediction to create a picture of the external world. This creates a dynamic internal model that can impact on neuronal activity in sensory systems, increasing activity to unpredicted events through a

[1] Belzeaux R, Cermolacce M, Jardri R. Hallucinations: toward a dialogue between phenomenology and brain imaging research. *J Conscious Stud* (Forthcoming).

failure of this predictive mechanism, with consequent alterations in subjective perception and elaboration into delusional belief formation (64).

Finally, these recent models suggest a number of cortical and subcortical brain networks involved in the experience of AVH and that verbal hallucinations involve hyperactivity in secondary and primary auditory cortex, accompanied by disrupted coupling with the cognitive processes associated with monitoring/reality testing.

Neuroimaging Studies

Structural Brain Imaging

Structural imaging studies (i.e., studies investigating the brain morphology) have identified subtle but robust reductions in the gray matter volume (GMV) in patients with AVHs, particularly in areas involved in speech and language. Altered GMV in the superior temporal gyrus (STG) has been highlighted by both priori-defined region of interest (ROI) analyses (65) and voxel-based morphometry studies (66). Modinos et al. demonstrated that AVHs severity was significantly associated with GMV reduction in the left STG, including the Heschl's gyrus. Structural changes have also been identified in Broca's area and its homotopic contralateral area (67) and the primary auditory cortex (Heschl's gyrus) (68). In addition to reductions in GMV in language regions, numerous studies have reported modifications in other brain areas, such as temporal and frontal regions (69), insular cortex (70, 71), thalamus (72), and cerebellum (73).

In addition to these quantitative analyses, structural imaging also provides complementary qualitative measures of the cortical morphology, such as the shape of sulci and gyri (74). Indeed, gyrification is considered an indirect marker of brain development since cortical folding (i.e., gyrification and sulcation) begins in the tenth week of gestation and stabilizes by the end of the third trimester of pregnancy. The resulting complex sulcal/gyral patterns are then stable over life (75). Studying changes in cortical morphology associated with AVHs provides a novel way to assess the impact of developmental factors on this symptom (76). Significant reductions in the gyrification of language-related areas (e.g., the superior temporal ridges, the left middle frontal sulcus, Broca's area) have been identified in chronic schizophrenia patients with AVHs when compared with healthy controls (77). The phenomenology of AVHs has also been associated with morphological changes within the language network. Indeed, the spatial location of AVHs (as internal or external percepts) has been associated with specific sulcal deviations in the right temporoparietal junction (78).

Functional Brain Imaging

Functional brain imaging studies in patients with AVHs have provided information about the neural bases of the susceptibility to hallucinate (trait studies), and neural activation that is seen during AVHs (state studies).

Trait Studies

Trait studies measure brain activity during specific tasks in patients who hallucinate and those who do not. Inquiring afterward for the absence of AVHs while scanning is necessary to avoid any "state" factor to interfere with this type of paradigm.

Trait studies have revealed altered functional activity in the temporal lobes of patients with AVHs (8, 79). Altered activation is thought to emerge from a competition between AVHs and normal external speech for processing sites within the temporal cortex (80). Similarly designed studies have identified a decrease in the functional activity of the rostral dorsal ACC, a structure known to be involved in the allocation of an internal or external origin for a given stimulus (81, 82). These results are not only compatible with the misattribution models of AVHs (see Neurocognitive Models) but also with recent structural data (83).

State Studies

Functional brain imaging suggests that a distributed network of brain regions underlies the experience of AVHs (84). Speech production and comprehension areas have been shown to be involved, but in addition to this network, brain areas involved in contextual memory seem to play a role in AVHs. This was notably revealed by a coordinate-based meta-analysis of AVHs capture studies, which demonstrated increased activity in Broca's and Wernicke's areas, and also in the hippocampal complex (84), suggesting that hallucinations could result from the aberrant activation of memory traces within associative cortices (85, 86). Although it is still a subject of debate, the activation of the primary auditory cortex does not appear to be necessary for the occurrence of AVHs. Nonetheless, its activation could be related to specific phenomenological aspects of the hallucinatory experience, such as the feeling of reality (87).

Connectivity Studies

Brain connectivity can be studied using three different approaches: functional connectivity, effective connectivity, and structural connectivity (88). Functional connectivity relies on correlation measures between spatially distant brain areas without information on the directionality or causality of the interaction. In contrast, effective connectivity explores the direct influence of one brain region on another, and thus provides information regarding the causal relationship between brain areas in a given network. Finally, structural connectivity is the measure of white matter tracts connecting different brain regions, based on diffusion MRI and tractography algorithms. Many connectivity studies have confirmed the dysconnectivity hypothesis in schizophrenia patients and in particular those who report hallucinations. Indeed, abnormal connectivity between brain regions has been shown at rest [for review, see Ref. (89, 90)] and during verbal tasks by functional and effective connectivity studies (91, 92). This dysconnectivity appears to play a major role in the emergence of hallucinations but was also found to change according to the sensory-modality involved (93, 94). Diffusion MRI studies comparing patients with schizophrenia who experience hallucinations, non-hallucinating patients with schizophrenia, and healthy controls have found differences in the coherence of the white matter bundles connecting language areas (68, 95, 96). This finding was particularly noteworthy in the arcuate fasciculus (97).

WHAT STRATEGY TO RELIEVE AUDITORY-VERBAL HALLUCINATIONS WITH fMRI-NEUROFEEDBACK?

In this section, we propose three different fMRI-NF strategies dedicated to AVHs' treatment on which our teams are currently working on (see **Figure 2**). We focus on the localization of the target and the type of feedback used for each strategy.

Strategy 1: *A Priori* Target Localized Using Structural MRI

Method Used to Localize the fMRI-Neurofeedback Target

During fMRI-NF protocols, the brain region(s) from which the NF signal is derived can be informed anatomically using structural MRI data and brain atlases (e.g., Talairach and Tournoux coordinates) or according to macroscopic anatomical landmarks. This method is the easiest to implement methodologically but assumes a good understanding of the underlying neural mechanisms and their anatomical location. The goal is to regulate neural activity in areas that show aberrant activations during AVHs (e.g., Broca's and Wernicke's areas) or to regulate activity in regions thought to be involved in compensatory or resilience processes (e.g., ACC). Below, we present an fMRI-NF protocol targeting the ACC (see **Figure 2**, Strategy 1).

Why Choose ACC as a Target for fMRI-Neurofeedback to Relieve AVHs?

Disrupted connectivity between the temporal and cingulate cortices has been demonstrated in schizophrenia, with AVHs severity correlating with the connectivity strength between the ACC and the STG (98, 99).

The ACC has a key role in regulating emotions, goal-directed behaviors, attentional processes, response selection, online source monitoring, and cognitive control (100, 101). Moreover, the ACC is involved in differentiating between self- and non-self related stimuli (82, 102). Furthermore, a meta-analysis of trait studies conducted in patients with AVHs and healthy controls revealed decreased ACC activity in hallucinators (79). This finding is in line with cognitive models of AVHs (30, 87).

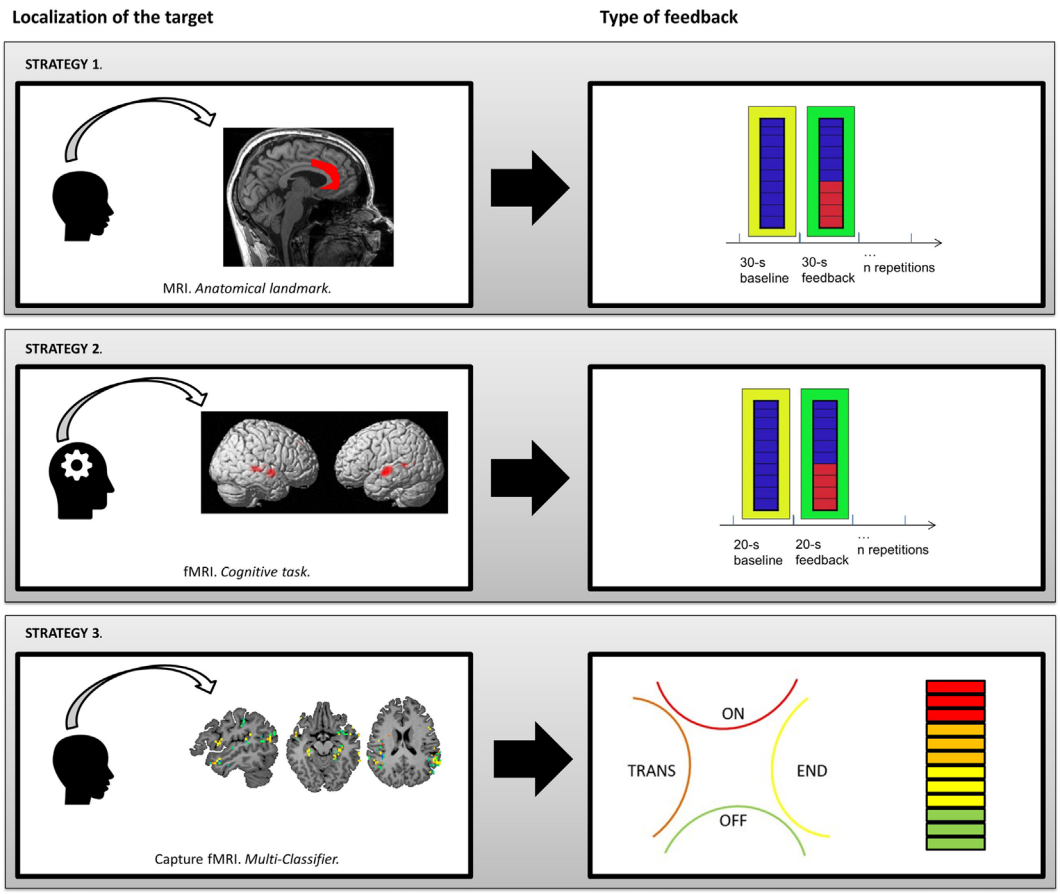

FIGURE 2 | Presentation of three different strategies for fMRI-neurofeedback protocols to relieve AVHs. Strategy 1: co-registration of anatomical template of anterior cingulate cortex. Strategy 2: human voice responsive auditory cortex identified with a functional localizer. Strategy 3: linear Support Vector Machine discriminative maps of a classifier after recursive feature elimination steps, which is able to detect neural patterns associated with hallucinations in resting-state brain activity with a level of accuracy of 71%.

A number of studies have demonstrated that the ACC can be reliably regulated using fMRI-based NF (13, 17, 103–106). Moreover, the successful upregulation of the rostral ACC was associated with an increase in positive affect (103, 106) and improved emotional perception of voices in healthy subjects (103).

Even though the theoretical accounts differ in the different studies (see Neurocognitive Models), they all assume a failure of typical ACC functions. The monitoring of inner speech processes, the monitoring of retrieval processes and error detection, as well as the suppression of task-irrelevant stimuli are all classical ACC functions that should be fostered by an upregulation of the ACC (107, 108). However, two previous studies report increased ACC activation during hallucinations (58, 109). It is possible that increased ACC activation may be related to default-mode fluctuations, considering simultaneous deactivations of auditory cortex and Wernicke's area in the former study and resting-state activations without baseline subtraction in the latter study.

The fMRI-Neurofeedback Protocol

First, an anatomically predefined ACC mask is applied. From this ROI, the average signal is fed back on a thermometer-like display after filtering and artifact reduction. A custom anatomical template mask of the ACC defines the ROI [details in Ref. (110)]. This ACC mask is taken as a part of the cingulate cortex excluding parts inferior or posterior to the anterior fissure. The feedback signal is the average BOLD signal across this ACC mask for each volume with 1% representing the full scale. A custom toolbox conducts online processing comprising motion correction and co-registration to a template (111). Kalman filter reduces singular values and high-frequency components. An exponential moving average algorithm removes temporal drifts.

The patient performs three fMRI-NF training runs, each consisting of eight regulation blocks and nine baseline blocks (30 s each; see exemplary run in **Figure 2**). Increase of ACC signal makes a green bar moving upwards and decreasing downwards [Ref. (30)]. A fixed red bar in the regulation condition serves as a regulation target. It indicates the upper limit of ACC upregulation. The baseline condition is indicated by a blue line display. Mental strategies should be tried to move the green line upwards to the red line. During the baseline blocks, the patient counts backwards from 100. Every repetition time (TR; 1 s), the display is updated. The NF procedure is explained to subjects, including the delay of the NF signal for 3–5 s due to the hemodynamic response and data processing (<1 s).

Preliminary Data

Patients with schizophrenia can learn to regulate the ACC to a comparable level than healthy controls, albeit involving different networks and cognitive strategies (30). Moreover, a recent article involving three schizophrenia patients suggests that even with ongoing AVHs, patients are able to learn ACC regulation (110). In this work, patients seemed to be very interested in the methodology and were eager to learn. Since the target groups were patients with long-standing symptoms, a core preposition was a good patient–therapist relationship and only limited impairments in cognitive functions. RWTH Aachen University is just performing a clinical trial study investigating the effect of fMRI-NF training in schizophrenia patients with ongoing AVHs.

Previous fMRI-NF studies have demonstrated that upregulation of a single area can elicit alterations of functional and effective connectivity (112, 113). Further studies may elucidate whether ACC upregulation also induces changes of the network dynamics. In the long term, it may be even more effective if fMRI-NF could target several regions aiming to regulate the functional connectivity between these regions. This would allow fMRI-NF to address the neural dysconnectivity that is proposed to underpin AVHs (114). This approach would also enable the regulation of connectivity and activity with the salience network, also proposed to be dysfunctional in people with AVHs (115–117).

Strategy 2: Region of Interest Defined Using a Functional Localizer

Method Used to Localize the fMRI-Neurofeedback Target

The target chosen for fMRI-NF can also be functionally defined. In this case, the patient is asked to undertake a functional task within the scanner, and activated areas are then used as the ROI(s) for fMRI-NF. The choice in the "functional localizer" task should be based on an *a priori* hypothesis that is well validated in previous studies.

Why Use a Functional Localizer for fMRI-Neurofeedback to Relieve AVHs?

As already mentioned, in schizophrenia, both state and trait brain imaging studies have revealed aberrant neural activation in patients with AVHs. Resting-state or "non-task" studies suggest that several speech-related areas are linked with such experiences, as well as the ACC and the hippocampal complex (see What Do We Know about the Neural Basis of Auditory-Verbal Hallucinations?). Similarly, task-related paradigms have identified frontotemporal dysconnectivity in patients with AVHs, specifically between the left STG and the dorsal ACC (99) and the medial prefrontal cortex (118), regions thought to be involved in self-other source monitoring. Disruption of these mechanisms is consistent with cognitive models that postulate aberrant bottom-up and top-down processes in AVHs.

Any of these regions could potentially be defined as a target to create a ROI mask for fMRI-NF. However, rather than using a structural or anatomically defined mask, a functional localizer task can be used to define the ROI (119). The choice of an appropriate task for the functional localizer should be informed by previous imaging studies, i.e., studies consistently discriminating the target ROI from other brain activity.

For example, two meta-analyses of AVHs in schizophrenia demonstrated that the human voice sensitive region of the left and right STG is associated with the experience of AVHs (66, 79). Therefore, this region could serve as a potential ROI mask (see **Figure 2**, Strategy 2). The functional localizer task would need to be designed to specifically identify the human voice responsive auditory cortex [i.e., the task reported in Ref. (120)]. This could be obtained by running of blocks of words (activation) and non-word speech analogs (baseline).

The fMRI-Neurofeedback Protocol

After completing data acquisition, the effective signal change measured within the functional localizer tasks is analyzed with univariate fMRI methods, such as the general linear model. The difference between the average BOLD signal of the activation block and the baseline block should be used to create the ROI mask. Several programs offer tools for online analysis, e.g., the AFNI software (http://afni.nimh.nih.gov/afni/). Here, the mask is created by eyeballing the resulting 3D cluster and manually specifying the statistical thresholds until a cluster of the required size/shape is present in the target ROIs. Ideally, the cluster size choice should be informed by previous meta-analytic studies. The mask should also include a control region to serve the averaging out of non-specific brain activation. A randomized controlled trial should also include a control group utilizing a control ROI mask, and each participant should complete both the target and control ROI localizer tasks, in spite of group assignment.

A new mask ROI can be created during each scan, or a retrospective method can be used, whereby the mask obtained during the first visit is used during subsequent neurofeedback trainings. The retrospective method requires the alignment of the different time-series data obtained from different scans. Some MRI scanners allow the realignment of previously obtained data with the current images. However, if this option is not available, most online analysis software have inbuilt algorithms that allow to realigning images obtained during different scanning sessions. The advantage of the retrospective method is the reduction of scanning time and therefore participant discomfort as well as global costs. In addition, the ROI mask does not change shape or size.

In terms of the neurofeedback training, this procedure remains the same as during anatomically masked ROI real-time fMRI, i.e., feedback is provided during the entire training run but remains static during rest (no-regulation blocks). Similarly, participants need to be informed about the inherent delay in feedback due to the hemodynamic response and adhere to standardized instructions. To enhance motivation and the likelihood of successful signal downregulations, participants are instructed to devise their own strategy to downregulate their signal (29, 121).

Strategy 3: Pattern Recognition Using a Multivariate Classifier

Method Used to Localize the fMRI-NF Target

The two previous strategies rely on imaging-based "trait markers" (i.e., persistent traits or vulnerability markers that can also be detected in the presymptomatic and remitted phases of mental disorders). The patient is trained to gain control of areas known to be involved in the AVHs' pathophysiology. When using such a methodology, the occurrence of hallucinations in the scanner during neurofeedback sessions is not necessary.

However, because hallucinations are acute symptoms, notably characterized by intrusiveness and phasic activity, they can also be targeted with a different type of strategy based on "state markers" (i.e., which correlate with symptomatic states). Here, the objective is to train the subject to self-regulate the activity of brain areas that reactivate during symptomatic states. Machine-learning, and particularly the recent development of "linear Support Vector Machine" (lSVM), offers several advantages in this context. Indeed, this technique classifies functional or anatomical patterns using a multivariate strategy. A training session allows the optimal classifier to be built on the basis of a training dataset, for which the periods of interest (e.g., symptomatic vs. asymptomatic) have been identified and provided (122). A validation session is then needed to test the performance and possible generalization of this classifier to new data based on an independent sample. Several interesting results for diagnosis or therapeutic response prediction purposes have been published, notably in bipolar disorder (123) or schizophrenia (124). However, this is not the only way to use such tools in psychiatry. Classifiers can quickly detect the emergence of subjective symptoms by detecting specific patterns of brain activity identified during symptomatic periods (see **Figure 2**, Strategy 3).

Why Use Classifiers for fMRI-NF to Relieve AVHs?

Using fMRI classifiers, it is now possible to detect the onset of subjective symptoms together with the associated brain activation patterns (125, 126). For example, our group developed such a classifier to detect AVHs occurrence while scanning a patient with a 71% accuracy (127). This algorithm is currently under optimization and already reaches 80% accuracy. Even if no data are currently available on the use of this kind of classifier in fMRI-NF protocols, the fine-grained activity patterns obtained could theoretically be used as the signal fed back to the patient. Future studies should allow specifying the minimal necessary accuracy.

However, to be eligible for this strategy, the patient's hallucinations must exhibit some specific features. The most important criterion is frequent occurrence. Indeed, the symptom must occur several times during the fMRI session. Moreover, data analysis and patient interviews must allow the identification of "symptomatic" and "asymptomatic" periods to build an efficient classifier. In our case, we chose to build a subject-independent classifier based on the AVHs presence or absence, determined with the methodology described in Ref. (87). This strategy presents substantial benefits compared with a subject-dependent pattern classification of fMRI signals, notably a considerable time-saving (128).

The fMRI-Neurofeedback Protocol

Unlike the two methods described above, this strategy does not imply a block paradigm. Indeed, the visual feedback provides an information in real time about the current state of the participant (hallucinating or not) all along the session. The visual feedback may be a thermometer whose signal intensity is based on the level of activation in the ROIs (given by the discriminative maps of the classifier). But, other possibilities emerged from recent work on AVHs. Our team recently proposed a method to distinguish between the different periods in the occurrence of AVHs (117). Even if we are at a very preliminary stage, this could theoretically allow for the implementation of a multi-classifier strategy with the possibility to discriminate multiple "brain-states" as, in our case, (i) "No hallucination" ("Off" period on **Figure 2**), (ii) "Transition" ("Trans" period on **Figure 2**; i.e., period immediately preceding the AVHs occurrence), (iii) "Hallucination" ("On"

period on **Figure 2**), and (iv) "End" ("End" period on **Figure 2**; i.e., period immediately following the AVHs occurrence). This technique can provide a feedback indicating which "brain-state" is identified. For example (as presented in **Figure 2**), a four-part diagram presenting the four brain-states can be used. If the "hallucination" period or "transition" period is identified, the participant must adapt his/her mental strategy to go back to "end" or "no hallucination" periods. This kind of feedback could also be combined with a thermometer display (to provide both a continuous and a discrete variable to the subject).

LIMITS AND FUTURE DIRECTIONS

fMRI-Neurofeedback Experimental Designs

The most obvious limitation of the available studies testing fMRI-NF protocols are their small sample sizes, making generalization difficult. For AVHs, no study assessing the efficacy of fMRI-NF is currently available. Nevertheless, the improved understanding of the neural underpinnings of AVHs seen in recent years and the preliminary results presented here should inform future studies.

The gold-standard to assess new treatments is the double-blind, randomized controlled trial design. However, a major issue in fMRI-NF protocols is to achieve complete "blindness" in patients, because an active collaboration is needed during the sessions. This directly questions what could be an ideal control condition? Four kinds of control conditions have been described in the literature (11) (i) mental task outside of the scanner, (ii) sham feedback using brain signal of interest from previous participant, (iii) sham feedback using inverse brain signal of interest, and (iv) sham feedback using brain signal from an unrelated region. The first solution appears unsatisfactory because patients in the control group are not exposed to fMRI-NF. Using a brain signal of interest from previous participants may generate frustration and retention since participants may unravel the non-contingency of the feedback, which would unblind them and reduce their engagement with the intervention. Moreover, for patients with severe AVHs, this kind of feedback could increase anxiety, letting them think that they have no control on their neural activity. Using an inverse brain signal of interest is unethical in the specific case of AVHs treatment. Indeed, this kind of sham feedback aims to test if inverse brain modulation prompts opposite behavioral changes. As a consequence, the expected change would be a worsening of AVHs symptomatology. Neurofeedback from a non-interest region should be the "least bad" solution for a control condition in fMRI-NF protocols to treat AVHs. The selection of a non-interest region appears crucial here and could be a difficult challenge, given the complexity (and spread) of the brain networks involved in AVHs (unfortunately, no data are currently available on the potential non-interest ROI that could be used for protocol, testing the efficiency of fMRI-NF in AVHs).

Another significant challenge to adequately assess neurofeedback effectiveness is to develop dedicated post-session scales that are able to identify the specific cognitive coping strategies used by the patients during the session. Such individualized strategies could then be applied in psychotherapy, potentially leading to the development of neuroimaging-guided programs. A rigorous evaluation of the strategies used to cope with AVHs during the fMRI-NF sessions could then be helpful to optimize general hallucination-focused psychotherapy programs. We believe that this may constitute an interesting two-way relationship between conventional psychotherapy and fMRI-NF: fMRI-NF is a precious tool to optimize hallucination-focused psychotherapy programs, while the identification of brain changes after psychotherapy allows for the identification of new neurofeedback targets.

Finally, testing whether brain self-regulation persists after the fMRI-NF protocols is a crucial issue. The "transfer session" (see **Figure 1**) may provide information about the capacity of participants to self-regulate the target region(s) without feedback. Furthermore, it will be very important to determine how long this capacity persists after the fMRI-NF and how long the clinical improvement is maintained. To date, no formal follow-ups of symptoms were conducted with the patients. The question of the potential long-term effects of these treatments is clearly under-assessed in *fMRI Brain–Computer Interface* research in general (113) and no data are currently available for patients with schizophrenia.

fMRI-Neurofeedback Protocols

In addition to the non-invasive nature of fMRI-NF, one of its prominent features is to put the patient at the heart of the process. On one hand, the active participation of the patient in fMRI-NF may contribute to the reinforcement of their feeling self-efficacy [which constitutes an important therapeutic factor (129)]. On the other hand, this active nature may be source of limitations in schizophrenia patients with strong negative symptoms, who may lack motivation. Although some data seem to indicate that patients suffering from schizophrenia are able to achieve voluntary control of their own brain activity during fMRI-NF (29, 30), these results need to be confirmed in studies with larger samples. Given the importance of motivation in neurofeedback protocols, it seems very relevant to consider factors interfering with reward processing, such as negative symptoms and antipsychotic medication. The effort required by patients to undergo the fMRI-NF training should not be underestimated as well as the mixed motivation of the patients, since there often exists some positive aspects to the hallucinatory experiences, which the patients may fear losing as a result of the training. Future research will have to determine what the best experimental settings/instructions are for patients suffering from refractory AVHs together with severe negative symptoms.

Considering task design, the most of fMRI-NF studies use a block design (i.e., alternating periods of upregulation or downregulation with rest periods during neurofeedback runs, see **Figure 1**). However, the optimal number of blocks per run, the ideal duration of regulation blocks, and the best number of sessions to obtain a maximal efficacy in the treatment of AVHs remain unknown. Future research should determine if patients suffering from schizophrenia (particularly those who exhibit severe cognitive impairment) may benefit from special arrangements in fMRI-NF protocols to minimize the attention span and the tiredness.

Informal reassessments during clinical visits that were conducted during the pilot study of the currently ongoing study with schizophrenia patients with AVHs (see above) revealed that none of the patients reported adverse events, and two of the patients claimed to have developed different strategies in dealing with their AVHs up to few weeks after the training (110). However, during contact and assessment occurring more than a month after the training, none of the patients had the impression that fMRI-NF training had had any influence on their symptoms. Individual variability and fluctuation in the disease course may override the – so far rather small – effects of the fMRI-NF training. This may change with better targeted fMRI-NF protocols. However, based on clinical impressions, we would suggest that at least monthly booster session would be advisable for clinical trials.

From a methodological point of view, uncertainty lies also about the instructions to be given before the session. It remains unknown if explicit (the participant is asked to use specific mental strategies for self-regulation) or implicit (the participant is only asked to upregulate or downregulate with the feedback provided) instructions should be preferred. Implicit instructions are ideal in general population, because they favor the development of individualized strategies to achieve voluntary control of the target region(s). However, the identification of an optimal strategy may be difficult for patients with severe AVHs, which could lead to a rapid decline in motivation. That is why providing specific explicit strategies could be useful to enhance the efficacy of fMRI-NF to treat AVHs. Strategies inspired from CBT could allow the participant for achieving voluntary control more quickly.

Finally, considering the definition of the fMRI-NF target, many other neural networks may serve as target for the fMRI-NF training. Interestingly, one of the most robust effects of fMRI-NF training seems to be changes in connectivity [e.g., Ref. (112, 130)]. Indeed, the first fMRI-NF studies attempt to train network connectivity directly (131, 132). Considering the importance of network function on the AVHs phenotype, connectivity fMRI-NF will be one of the next targets for treatment approaches to AVHs.

CONCLUSION

Although a number of studies are currently investigating the efficacy of fMRI-NF for AVH, as for today, efficiency data from randomized controlled trials are lacking (11). In this paper, we focused on specific fMRI-NF strategies to treat AVHs and selected three of them that appear most feasible, emphasizing the need for preliminary studies. Indeed, considering the potential cost necessary to implement fMRI-NF, proof-of-concept studies are urgently required to define the optimal strategy for application in patients with AVHs. This technique has the potential to establish a new brain imaging-guided psychotherapy for patients that do not respond to conventional treatments and take functional neuroimaging to therapeutic applications.

AUTHOR CONTRIBUTIONS

TF, NO, MD, PA, KM, and RJ equally contributed to the manuscript writing.

ACKNOWLEDGMENTS

TF is partially supported by a doctoral fellowship from the *Pierre Deniker Foundation*.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 21 June 2016
doi: 10.3389/fpsyt.2016.00111

Real-Time fMRI Neurofeedback with War Veterans with Chronic PTSD: A Feasibility Study

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Many patients with post-traumatic stress disorder (PTSD), especially war veterans, do not respond to available treatments. Here, we describe a novel neurofeedback (NF) intervention using real-time functional magnetic resonance imaging for treating and studying PTSD. The intervention involves training participants to control amygdala activity after exposure to personalized trauma scripts. Three combat veterans with chronic PTSD participated in this feasibility study. All three participants tolerated well the NF training. Moreover, two participants, despite the chronicity of their symptoms, showed clinically meaningful improvements, while one participant showed a smaller symptom reduction. Examination of changes in resting-state functional connectivity patterns revealed a normalization of brain connectivity consistent with clinical improvement. These preliminary results support feasibility of this novel intervention for PTSD and indicate that larger, well-controlled studies of efficacy are warranted.

Keywords: PTSD, war veterans, neurofeedback, real-time fMRI, resting-state, functional connectivity

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Klaus Mathiak, RWTH Aachen University, Germany
Thomas Koenig, University Hospital of Psychiatry, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *24 December 2015*
Accepted: *06 June 2016*
Published: *21 June 2016*

Citation:
Gerin MI, Fichtenholtz H, Roy A, Walsh CJ, Krystal JH, Southwick S and Hampson M (2016) Real-Time fMRI Neurofeedback with War Veterans with Chronic PTSD: A Feasibility Study. Front. Psychiatry 7:111. doi: 10.3389/fpsyt.2016.00111

INTRODUCTION

Post-traumatic stress disorder (PTSD) is among the most impairing and common of psychiatric conditions, with a lifetime prevalence of 8–10% and a 12-month prevalence rate between 3.7 and 4.7% (1, 2). Yet, extant data indicate that about 30–50% of patients do not respond to current evidence-based psychological therapies or pharmacological interventions, and some subgroups (such as combat-exposed patients) show even higher rates of treatment-resistance and drop-out [(3, 4); Institute of Medicine Report]. Over the last few decades, despite the dramatic growth in the literature of the neurobiological underpinnings of PTSD, very few neuroscientific discoveries have been translated into effective and novel treatments (5). Currently, the most effective interventions have been informed by psychological theories and behavioral data (such as cognitive behavioral therapy (CBT) and other trauma-based therapies) (5, 6). Pharmacological interventions for PTSD, such as selective serotonin reuptake inhibitors (SSRIs), which were introduced due to their antidepressant effects, have demonstrated modest treatment response (5). To date, only two medications, both selective SSRIs, have FDA approval for the treatment of PTSD. In civilian treatment seeking populations, fewer than half of patients achieve full remission on SSRIs. The rates of non-response or partial response to these medications among combat-exposed military, particularly those with

chronic PTSD are comparable or worse to those of the civilian patient population (7–11).

Therefore, it is paramount that we begin to bridge the gap between neurobiological findings of PTSD and clinical practice. The development of neuroscientifically informed treatments has the potential to complement and enhance current interventions, thus increasing treatment effectiveness and reducing treatment-resistance and drop-out rates (12, 13).

A few studies have investigated the potential of electroencephalography (EEG) neurofeedback (NF) as a neuroscientifically informed intervention for PTSD (14–16). Although EEG NF has important features, it has the limitation that targeting specific brain areas, such as the amygdala, is difficult if not impossible with EEG. As our understanding of the brain circuits involved in PTSD and other disorders advances, there is increasing demand for a NF technique that can more directly leverage neuroscientific knowledge by allowing us to target specific brain areas. Real-time fMRI neurofeedback (rt-fMRI NF) presents this opportunity.

Real-time fMRI neurofeedback is a relatively new technique that allows us to target localized brain areas (or to entrain specific spatial patterns of brain activity), providing a wonderful opportunity for developing neuroscience-guided, targeted interventions. In rt-fMRI NF, participants receive contingent visual (or auditory) feedback about a specific aspect of their brain activity pattern, and practice trying to control that aspect of their brain function using feedback as a training signal (17, 18). Many studies have shown that rt-fMRI NF training can be used to teach participants to exert volitional control over their own neurophysiological response (18–21). In a variety of subject populations, participants have used rt-fMRI NF to successfully regulate activity in the amygdala, anterior cingulate, and insula, among other brain regions and circuits (19, 21–23). As participants learn to modulate their brain response, it has been shown that behavioral and neurophysiological changes occur that are specific to the brain region or network targeted during the NF (21, 24–30). Due to the ability of NF to modify cognition, behavior, affect, and neurophysiology, the potential applications of rt-fMRI NF are being investigated in clinical treatment settings (31, 32). Current literature suggests that rt-fMRI NF may be able to reduce symptom levels and also normalize brain activity across diverse psychiatric and neurological conditions (21, 27, 28, 33–41).

To the best of our knowledge, this pilot study represents the first attempt to test the viability of rt-fMRI NF for PTSD. Three Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) veterans with chronic PTSD (i.e., more than 3 months) were recruited and underwent three rt-fMRI NF training sessions (of about 30 min each). A functionally localized region of the amygdala was targeted during NF due to (i) its well-established involvement in PTSD pathophysiology, hyperarousal, and anxiety (42–45) and (ii) because extant rt-fMRI NF data suggest that subjects can learn to modulate its activity level (23, 41). In particular, participants were trained to modulate their amygdala activation during a symptom provocation paradigm (i.e., participants listened to audio-recorded narratives of their own traumatic memories). By training participants to control emotion-related brain activity patterns that are activated during trauma recall, the intervention directly targets a possible neural correlate of their symptomatology. In addition to clinical symptom assessment before and after the NF, functional neuroimaging data pre- and post-NF training were also collected. Although any clinical intervention should ultimately demonstrate effectiveness by reducing symptoms and/or increasing well-being, incorporating neurophysiological data as an outcome variable in clinical trials is recommended as a means of better elucidating treatment response (12, 46, 47).

The overarching aim of this pilot research project was to investigate the clinical feasibility of rt-fMRI NF with a highly vulnerable patient population with chronic PTSD. There were three main hypotheses. First, it was hypothesized that all participants would tolerate the intervention well. This was expected because (i) neuroimaging studies have used symptom provocation paradigms with PTSD patients (48, 49), (ii) various studies using other NF techniques (e.g., EEG NF) showed that NF is feasible with PTSD patients (14–16), and (iii) studies of rt-fMRI NF have been successfully performed with other patient populations that show disturbances in affect regulation and cognition (37, 38, 41, 50). Second, in line with other clinical NF studies, it was hypothesized that, post-intervention, patients would show a reduction in symptoms (15, 27, 28, 31, 37, 38, 50). Third, it was hypothesized that normalization in resting-state functional connectivity (rsFC) of the amygdala would occur (51–57). In particular, rsFC changes were expected to be consistent with those found in other PTSD resting state and intervention studies that used neuroimaging data as an outcome measure (58). In particular, we expected to find (i) an increase in rsFC between the amygdalae and regulatory medial and orbitofrontal areas, and (ii) a decrease in rsFC between the amygdalae and limbic regions and salience network areas.

Importantly, if these hypotheses would be satisfied, only the feasibility, but not the efficacy, of this treatment would be established. At this stage, any post-intervention changes in functional connectivity or symptoms cannot be attributed directly to the NF. For such causal inference to be made a larger sample and the presence of a control/placebo group would be necessary.

MATERIALS AND METHODS

Design

This pilot study investigated the feasibility of rt-fMRI NF for treating PTSD patients. A short-term longitudinal design was adopted in order to measure symptoms and rsFC changes before and after the NF intervention. No control group was used for this unblinded pilot intervention.

Participants

Three OIF/OEF/OND veterans with chronic PTSD were recruited through the Veterans Affairs (VA) Connecticut Healthcare System, in West Haven, CT, USA. The three participants will be referred to as participant A, B, and C. Participants received compensation for their time and travel expenses. The study was performed in agreement with a research protocol approved by the Human Research Protection Program at Yale University and the Human Subjects Subcommittee at the VA Connecticut Healthcare System. Subjects provided written consent at both institutions.

Entry criteria included (i) a formal diagnosis of PTSD, as confirmed by the Clinician Administered PTSD Scale (CAPS) and with a total severity score of ≥50; (ii) chronic PTSD symptoms for at least 1 year; (iii) no concurrent Axis I disorders at the time of assessment, with the exception of non-threshold mood and anxiety symptoms; (iv) concurrent psychotropic treatments only if participants were on stable doses for at least 3 months; (v) no new behavioral treatments initiated for the past 3 months; and (vi) meeting the standard safety requirements for MR scanning.

Measures

Behavioral Measures

Demographics

Clinical records regarding current and past PTSD-related treatments were available through the VA Connecticut Healthcare electronic medical record system. Patient demographic information was also collected, including age, handedness, gender, ethnicity, education, and employment status.

Structured Interviews

Post-traumatic stress disorder symptoms were assessed (past-month and life time) using the CAPS for DSM-IV-revised 1998 (59). The CAPS was administered by experienced raters who demonstrated excellent inter-rater reliability (i.e., Kappa coefficients were between 0.80 and 0.90 for all interviewers). The Structured Clinical Interview for DSM IV-TR (SCID) was also administered to assess for comorbid Axis I disorders (60).

Questionnaires

The Combat Exposure Scale (CES) (61) was administered to assess combat exposure. (i) The Beck Depression Inventory, version II (BDI-II) (62), (ii) the military version of the PTSD checklist (PCL-M) for DSM-IV (63), and (iii) the State-Trait Anxiety Inventory (STAI) (64) were used to assess, respectively, depression, PTSD, and anxiety symptoms.

Trauma Scripts

A similar procedure to that described by Lanius et al. (65) and Pitman et al. (66) was used to generate the trauma imagery scripts. Briefly, in collaboration with each participant, script narratives from their six most traumatic life events were created and ranked from most to least traumatic. Two different scripts were formulated for each trauma memory (i.e., different wordings and descriptions). The scripts were rich in imagery, narrative accounts as well as descriptions of the emotional and physiological states experienced during the traumatic event (e.g., sweaty hands, tense muscles, etc.). The scripts were recorded by the same male voice across all participants. The recordings were then edited so that each single trauma script would last exactly 60 s. Then, six audio recordings of 286 s were produced and played back to the participants during the NF runs. Each NF recording contained 26 s of silence, 60 s of trauma script, then 70 s of silence, then 60 s of a different trauma script (of similar traumatic intensity), and again 70 s of silence.

Magnetic Resonance Imaging Data Acquisition Protocol

All magnetic resonance imaging (MRI) data acquisition was done using a 1.5-T Siemens Sonata scanner (Siemens Medical Systems, Erlangen, Germany). When imaging regions with high susceptibility, improvements in signal with increasing scanner strength are offset by increases in the susceptibility artifacts. In previous work, we optimized a NF protocol on our 1.5-T scanner for training people to control signal from high susceptibility regions of the brain (67). As the amygdala is also a region of susceptibility, we used the same scanner and sequence in this study.

Structural Image Acquisition

Every scanning session started with a structural localizer scan. During the first scanning session, the structural localizer was followed by a high-resolution sagittal scan, collected using a magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2400 ms; TE = 3.54 ms; TI = 1000 ms; flip angle = 8°; matrix size = 192 × 192; FoV = 240 mm^2; voxel size = 1.3 mm × 1.3 mm × 1.2 mm; Bandwidth = 180). This was used to register data to the Colin brain, thereby transforming it into the Montreal Neurological Institute (MNI) coordinate system (68). On the following scanning sessions instead of the high-resolution structural image (MPRAGE), a short lower-resolution sagittal T1-weighted scan was collected. This sagittal scan is required for slice alignment.

Then a T1-weighted spin echo axial-oblique anatomical scan (i.e., conventional anatomical scan) was collected with 31 contiguous, 3.1 mm-thick AC-PC aligned axial-oblique slices with coverage extending up from the bottom of the cerebrum (TR = 537 ms; TE = 11 ms; flip angle = 90°; matrix size = 256 × 256; FoV = 200 mm^2; voxel size = 0.8 mm × 0.8 mm × 3.1 mm; bandwidth 130). This structural image is necessary for registrations of the functional data into higher resolution space (i.e., MPRAGE image) and for the registration of the target and control regions (used during the NF).

Functional Imaging

The collection of structural images was followed by the acquisition of functional data at the same slice locations as the axial-oblique T1-weighted data. All functional images were acquired using a T2*-sensitive gradient-recalled single shot echo-planar pulse sequence (TR = 2000 ms; TE = 30 ms; flip angle = 80°; matrix size = 64 × 64; FoV = 200 mm^2; 3.1 mm × 3.1 mm × 3.1 mm; interleaved acquisition; bandwidth = 2604). The collection of functional images began, during every scanning session, with a short functional run from which a single volume was extracted to be used as the functional reference volume. A longer, but otherwise identical, functional data acquisition protocol (143 volumes, 286 s) was used also for all the other functional data acquisitions, including (i) two resting-state runs collected during every scanning session (i.e., two resting runs of 4 min and 46 s each), (ii) the functional localizer run used to select the region of interest (ROI) to be targeted during the NF sessions, and (iii) the real-time NF runs.

Image Data Processing

Images were motion corrected using SPM (http://www.fil.ion.ucl.ac.uk/spm/). Except where noted, all other analyses (i.e., real-time processing, t-maps for functional localizers, and seed-connectivity maps) were conducted using Yale BioImage Suite software package (69). All t-maps were smoothed using a 6-mm full-width at half maximum Gaussian kernel. All registrations were visually inspected.

Real-Time fMRI Data Acquisition Protocol

All subjects underwent three separate NF scanning sessions in which the target ROIs within the amygdala were functionally defined. The functionally defined ROIs were based on functional localizers (i.e., a trauma audio-script and frightening movie scenes) during the first scanning session for each subject.

Regions of Interest

For a detailed description of functional ROI processing, see the procedure described by Hampson et al. (67). Briefly, after the first scanning session, the data from the functional localizer were analyzed using the general linear model (GLM) to identify the 30 most active voxels within the amygdalae (with a cluster threshold of four voxels) to anxiety provoking stimuli (sometimes a scary movie was used and sometimes a personal trauma). The selection of the 30 voxels was done with a customized MATLAB program before the first NF session. At the start of each NF session, the ROI was transformed from the functional space in which it was defined (that is, the functional space of the first day when the functional localizer was collected) into the anatomical space of that same day via a rigid registration with nearest neighbor interpolation.

A control region, which included all the white matter, was defined by transforming the white matter from the template MNI brain into the patient's same anatomical space used during the target ROI registration. The white matter is chosen as a control region during the NF to control for global drift and arousal levels. The real-time analysis program used these two regions during the NF sessions. To adjust for global signal fluctuations in the real-time data, we followed the approach introduced by deCharms et al. (21) and plotted the percent signal change from the running mean of the target region minus percent signal change from the running mean of the control region.

Real-Time Pre-Processing

After the anatomical images were collected, the target ROI and the white matter control region were translated into the functional space of the current scanning day via a concatenation of two rigid registrations. First, the anatomical space of the first day was mapped to the anatomical space of the current day. Then, the anatomical space of the current day was mapped to the space of the functional reference scan of the current day. Once the ROI and the control region were registered into the functional space of the current scanning session, the real-time NF could begin.

Real-Time fMRI System

The rt-fMRI system that provides visual feedback during the NF scans is described extensively in two previous published studies (27, 28, 67).

Procedure

Timeline

Prior to the NF intervention, subjects completed all questionnaires, the SCID and the CAPS were administered, and the trauma scripts were created.

The CAPS clinical interview was conducted between one to 3 weeks prior to and after the NF training. Within 1 week before and after the NF training, the baseline and post-intervention resting-state scans were collected. On the day of these resting-state scans, before entering the MRI scanner, participants completed the PCL-M, the BDI-II, and the STAI. The NF sessions took place every 2–4 days (so the sequence of three sessions lasted 7–9 days depending on the participant). On each NF training day, before entering the scanner, participants also completed the PCL-M, BDI, and STAI.

Scanner Procedure

During each scanning day, participants completed the PCL-M, BDI-II, and STAI questionnaires before entering the scanner (note that the BDI and STAI scores will be presented only in the online Supplementary Materials document – in Figures S1 and S2 in Supplementary Material). Once in the scanner, the functional image acquisition began with the resting-state runs. The light was dimmed in the scanner room and subjects were required to rest for about 10 min with their eyes open (~5 min per resting run). On the first day, the resting-state runs were followed by the functional localizer runs (i.e., used to create the target ROI). During functional localizer runs, participants watched movie clips with frightening scenes or listened to a trauma audio-script for the activation blocks and rested for the baseline periods. Participant B also had two NF runs on this day (targeting the right amygdala defined anatomically).

After the first scan, all participants completed three NF scanning days where they received NF from a functionally defined region of the amygdala (bilaterally or unilaterally, depending on where the 30 most active voxels were during the functional localizer scan). Participants received detailed instructions before entering the scanner for the first NF session and received another brief reminder before the first NF run during each NF scanning day. Briefly, participants were informed that the line on the screen (**Figure 1**) represented the real-time activity (with about 4–6 s delay) of their own amygdala, an area of the brain where activity tends to increase when one is anxious. Participants were also told that an arrow at the top of the screen would cue them as to their current task throughout the run (**Figure 1**). A white arrow pointing forward would indicate a rest period (no task), a red arrow pointing up would indicate they should listen to the script and allow their amygdala activity to increase, and a blue arrow pointing down would cue them to try to decrease activity in their amygdala (**Figure 1**). The feedback was provided in the form of a line graph at the center of the screen. The line graph showing them their brain activity pattern was color-coded to match the arrows, so the line segments drawn during the rest block were white, those drawn during the increase/provocation block were red, and those drawn during the decrease block were blue (**Figure 1**). It was emphasized to the patients that they should bring the blue line down or at least stop it from increasing.

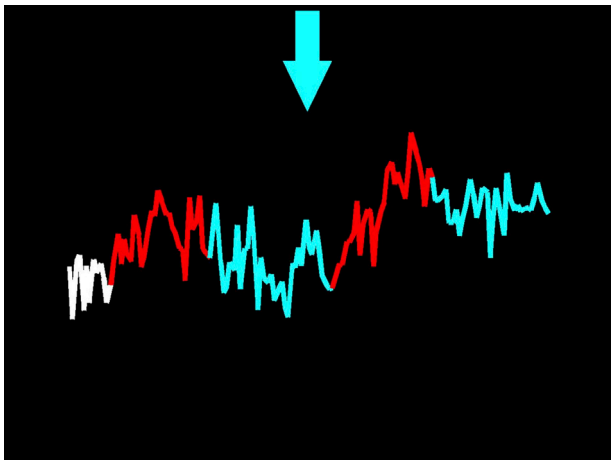

FIGURE 1 | Screen capture of the display a participant viewed taken at the end of a neurofeedback run. The participant heard personalized trauma scripts during the red/increase periods, and silence during the blue/decrease and white/rest periods. Their task was to bring the line back down in the blue blocks.

During each NF run, a 286-s audio file was played to patients (see Trauma Scripts for description of these files) while they viewed NF on the display screen. First, participants rested for 26 s at the very beginning (this, as explained above, was indicated by the white arrow). Then, as they listened to the first trauma audio-scripts (60 s), they were cued to allow their amygdala activity to increase (shown by the red arrow pointing upwards). When the trauma audio-script stopped, the participants were cued to decrease activity for 70 s (indicated by a blue arrow pointing down, as shown in **Figure 1**). Then, a second 60-s trauma script was played during which they could allow their amygdala to increase, and this was followed by the last period of attempted reduction of amygdala activity (70 s). Participants were allowed and encouraged to use any strategy to help them decrease activity. Participants completed five to six NF runs (of 286 s each) during each NF session (i.e., about 30 min in total). Trauma scripts were ranked from least traumatic to most traumatic. Participants began each NF session with runs in which they only heard the less traumatic scripts. How quickly each participant progressed to more traumatic scripts was determined by the patient. This self-paced approach was designed to maximize the comfort and sense of control experienced by the participant. However, all participants were able to use, at least on the last two NF scanning days, the most traumatic audio-scripts.

After completing all of the NF sessions, subjects returned for one final scanning session in which only resting-state functional data were collected, in order to allow comparison of resting-state data before and after NF.

Data Analysis

Behavioral Data

Due to the small sample size, no formal statistical or group analysis was performed on questionnaires and clinical interview data. Rather each subject was used as their own control for the analysis. In particular, symptom changes were calculated for each individual and compared to standardized threshold guidelines for clinical and statistical significance.

Offline Analysis of Resting-State Functional Connectivity Data

In addition to motion correction (see Image Data Processing), preprocessing involved regressing from the data time-course signals of no interest, including (i) cerebrospinal fluid and white-matter signals, (ii) subject motion parameters, and (iii) temporal drift, as well as low-pass filtering (<0.1 Hz). Resting-state data were analyzed using a seed-based FC approach. Specifically, a ROI-to-whole-brain connectivity analysis was performed. The ROI was created by transforming the bilateral amygdalae from the MNI brain into the subject functional space. This anatomically defined ROI was used rather than the functionally defined NF target region as the latter varied across individuals. Seed-connectivity maps were computed for the resting runs of each scanning session for each participant. These maps indicate how synchronized each voxel was with the amygdalae during the resting scans of that day.

Change maps in rsFC from the first scanning day to the last were created by first transforming both maps into the high-resolution anatomical space of the subject. Then, they were subtracted (last day minus first day) to yield a seed-connectivity change map. Finally, these seed-connectivity subtraction maps were analyzed at a group level by transforming all participants' maps to the common MNI space (via a non-linear registration) and adding them. No formal statistics were performed due to the small sample size and the exploratory nature of the study. Thus, an arbitrary threshold was set. The threshold was set such that 5000 voxels survived (in the high-resolution anatomical space) to allow examination of those regions showing the greatest change in connectivity after the NF training. This approach was used to identify peaks in the group map and was also used on the individual subject maps to explore which subjects showed the connectivity changes identified at the group level.

RESULTS

Demographics

Participants A, B, and C were adult males of 36, 46, and 30 years of age. All had a similar and moderate exposure to combat (i.e., participants A, B, and C scored, respectively, 22, 24, and 23 on the CES).

Participant's medical records indicated that participants A, B, and C had a formal diagnosis of PTSD, respectively, for 6, 2, and 3 years when enrolled in this study. Prior to this study, all participants underwent pharmacological and/or psychological treatments. In particular, participant A received 13 weeks of pharmacological treatment and several psychoeducation and mental-health visits at the VA prior to this study. participant B received 13 months of weekly individual psychotherapy prior to the NF intervention at the VA hospital. Participant C received a month-long in-patient care for PTSD followed by a full 12-week course of cognitive processing therapy at the VA hospital. He also received concomitant pharmacotherapy.

During the intervention, participants A and C were on a stable pharmacological dose (for at least 3 months before the intervention started), and participant C was attending individual counseling and group peer-to-peer psychotherapy (initiated more than 3 months before the intervention). At the time of the study, participant B was not receiving any pharmacological nor psychological treatment.

Behavioral Findings

PTSD Symptoms

CAPS Scores

Participants A, B, and C had total lifetime PTSD scores of 74, 83, and 88, respectively (i.e., severe-to-extreme symptom range) (70).

The past-month CAPS total scores before and after the intervention are shown in **Figure 2**. According to the CAPS diagnostic categorization (70) before NF training participants A and B with scores of 55 and 59, respectively, belonged in the moderate symptom range (40–59) and participant C, with a score of 81 was in the extreme symptom range (80+).

According to Weathers et al. (70) diagnostic categorization of PTSD symptoms, an asymptomatic clinical presentation is defined as a total score of below 20 on the CAPS. A 10-point decrease in the CAPS total score is considered a reliable marker of clinically significant change (9). Participant B, with drop of 47 points and Participant C with a drop of 34 points had clinically significant improvements in PTSD symptoms (**Figure 2**). Moreover, participant B achieved asymptomatic presentation with a final CAPS score of 12. Participant A, with a drop of three points did not achieve a clinically meaningful change on the CAPS (**Figure 2**).

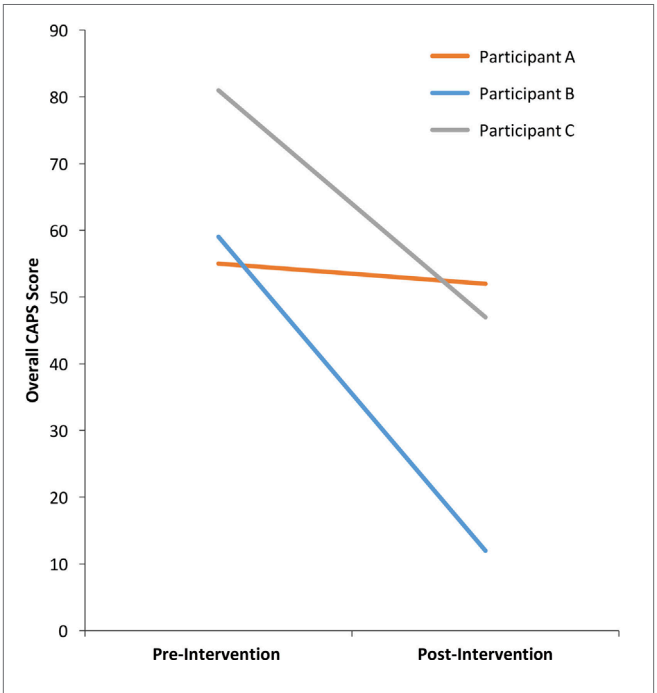

FIGURE 2 | CAPS scores before and after the NF intervention.

PCL-M Scores

Post-traumatic stress disorder symptoms were also monitored by the self-administered PCL-M questionnaire in each session. A PCL-M score in 17–33 range is considered to represent low symptomatology, a 33–44 range is considered moderate, and 44–85range is considered high (71). Empirical data suggest that a 5–10 point change is statistically reliable (on an individual basis), and that a 10–20 point change is clinically significant (71). Participant A had a reliable drop in severity score (i.e., five points) from 42 to 37 point, and both participants B and C had a clinically meaningful drop of 16 (from 37 to 21) and 13 points (from 45 to 32), respectively. Interestingly, all participants had the largest drop in severity of PCL-M scores after the first NF session (see **Figure 3**).

Neuroimaging Findings

Group-Level rsFC Changes post-NF

As shown in **Figure 4**, the group-level results from the resting-state seed-connectivity subtraction maps (i.e., last minus first scan) show a pattern of increased rsFC between the amygdalae and regulatory regions in the orbitofrontal cortex (OFC) and the ventral anterior cingulate cortex (vACC). Moreover, a reduction in connectivity between the amygdala and several salience network areas was observed, including the anterior insula, the dorsal anterior cingulate cortex (dACC), and temporal areas surrounding (and including) the amygdalae (for more details, see Table S1 in Supplementary Material).

Notably, the individual subtraction maps were qualitatively similar to the group-level map. Furthermore, none of the group-level findings were contradicted at an individual level (e.g., increased instead of decreased connectivity post-intervention).

DISCUSSION

This pilot study represents, to the best of our knowledge, the first investigation of the feasibility of rt-fMRI NF in PTSD patients. The main hypotheses were largely supported by our findings. First, all three participants tolerated the NF training well. Second, all patients showed some degree of improvement on the CAPS and PCL-M symptoms scores. Moreover, despite the chronicity of their PTSD symptoms, two participants experienced large (and clinically meaningful) symptom improvements. Third, the changes in rsFC post-treatment were consistent with normalization of PTSD-specific brain patterns across all participants.

Symptom Improvements

Clinician-Administered PTSD Scale and PCL-M scores provide different windows on symptom severity: the CAPS is a lengthy assessment involving a clinician, while the PCL-M is a brief self-report based measure. Importantly, recent evidence suggests that the PCL may be a more sensitive measure of clinical change than the CAPS in clinical trials (71). However, in this study, the patterns of symptom changes measured are generally consistent for the two measures. Differences in the clinical measures before and after the NF intervention suggest that large symptom improvements occurred for participants B and C who achieved

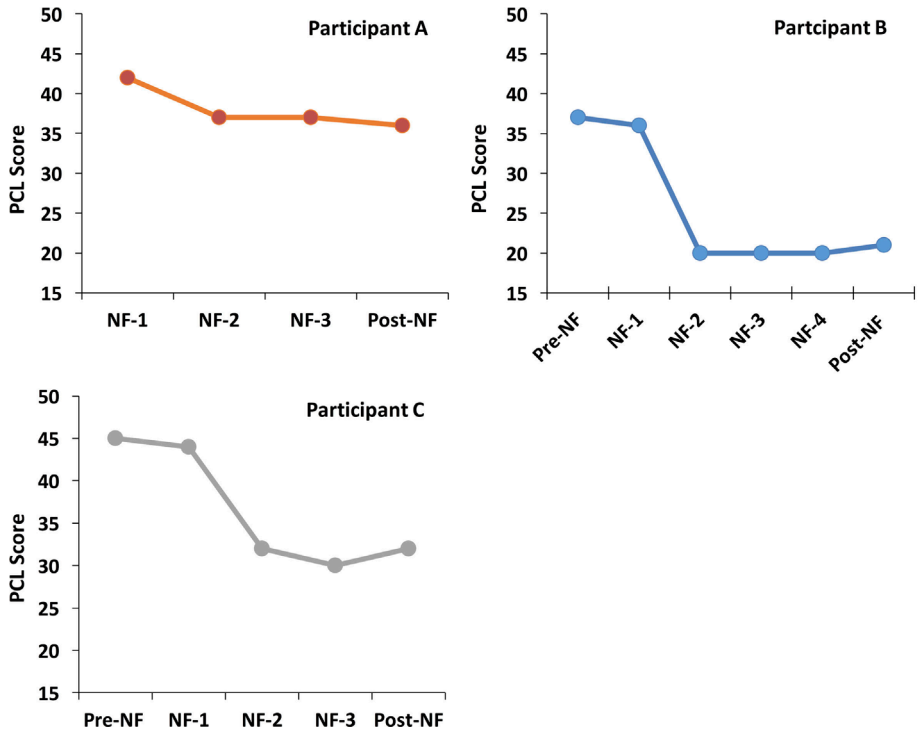

FIGURE 3 | PCL scores before, during, and after the NF training. NF-1 represents the PCL-M scores collected just before (but on the same day) as the first NF. Pre-NF represents assessments collected 1 week before the first NF. Post-NF represents data collected 1 week after the last NF session. All NF sessions shown for each subject were scheduled 3–4 days apart.

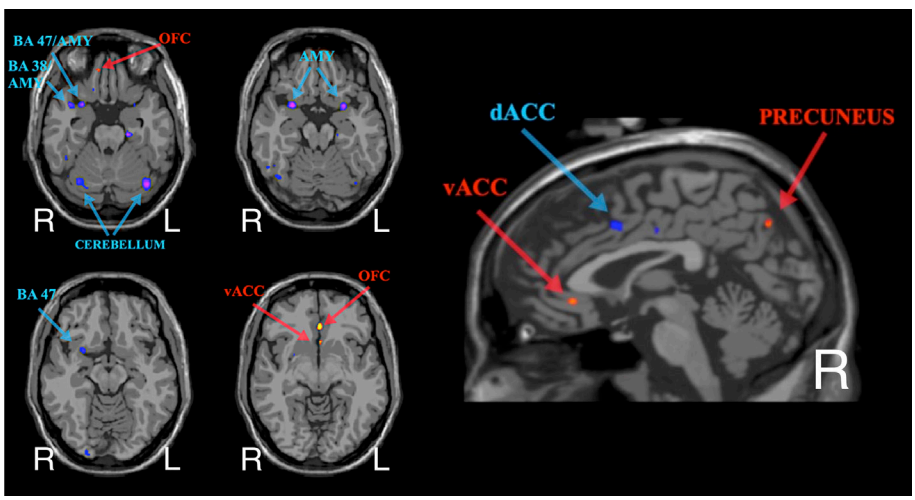

FIGURE 4 | Group-level average of subtraction seed-connectivity maps (ROI = bilateral amygdalae) showing the peaks in rsFC changes post-neurofeedback (in common anatomical space – i.e., MNI brain). Red/Yellow indicates an increase in rsFC, while Blue/Purple indicates a decrease.

substantial and clinically significant drops in CAPS severity scores, which were mirrored by clinically meaningful changes on the PCL-M. Moreover, post-intervention, with a final CAPS score below 20 points, participant B achieved an asymptomatic presentation. On the other hand, participant A achieved a smaller, yet reliable improvement on the PCL-M, and only a small drop on the CAPS score.

Interestingly, the PCL-M scores revealed that all participants consistently had the largest symptom drop after the first full session of functionally defined NF (NF-1 in **Figure 3**), which was

maintained during the following sessions and post-intervention. This suggests that the symptom improvements observed post-NF training are unlikely to be caused by random symptoms fluctuations over time. Although the largest symptom improvement followed the first NF session, it is unclear whether subsequent sessions may be important for consolidating that learning. Furthermore, as patients were not followed after the final CAPS assessment, it is unclear how long symptom improvements persisted. More research is needed to address these questions.

Changes in rsFC

Although the changes in rsFC in this study have not been corrected for multiple comparisons and, thus, should not be considered confirmatory, they are worth examining in a qualitative manner as they can inform future hypotheses. The similar patterns of changes in rsFC across participants suggest that the NF may have worked via consistent neurophysiological mechanisms. These changes included (1) increased rsFC between amygdalae and orbitofrontal/ventral anterior cingulate regions (OFC/vACC) and (2) decreased functional connectivity between amygdalae and other parts of the salience network.

Increased rsFC between amygdalae and OFC/vACC is consistent with the traditional neurocircuitry model of PTSD and with current understanding of PTSD pathophysiology (42, 43, 72). In particular, the disruption in the connectivity between regulatory frontal areas (including medial OFC and also the vACC) and the amygdalae is believed to underlie various PTSD symptomatology, such as hyperarousal and alterations in fear extinction processes (43, 72–74). Thus, the preliminary findings from this study suggest that this NF protocol may help to normalize fronto-limbic alterations in PTSD. Interestingly, this finding resonates with neuroimaging studies of other clinical interventions, suggesting that both behavioral and pharmacological interventions also facilitate the normalization of fronto-limbic circuitry in PTSD (75–80).

Decreased connectivity within the salience network is also highly consistent with neurobiological models of PTSD. Abnormally high levels of activity in salience network areas, such as the amygdalae, anterior insulae (AI), and dorsal ACC (dACC) have been linked with severity of PTSD symptoms, with treatment-resistance and also with increased familial vulnerability (42, 43, 81–84). As further evidence of the causal role of the salience network areas in the pathophysiology of PTSD, recent data suggest that positive responses to clinical interventions in PTSD are associated with reduced activity in regions of the salience network (especially the amygdala and dACC) (80). Also the rsFC literature has shown a consistent pattern of abnormally high connectivity within the salience network in PTSD (51, 54, 55). In line with the literature, the rsFC findings from this study revealed (both at an individual and group level) a decrease in rsFC between the amygdalae and other salience network hubs after the NF training. In particular, reduction in the amygdalae's rsFC were found with (i) the amygdala itself, (ii) with limbic regions bordering the amygdalae, including orbital cortex (BA 47) and the temporal pole areas (BA 38), (iii) with the brain tissues between (and including) the amygdalae and the AI, and also (iv) with the dACC.

One of the difficulties intrinsic to NF training is to target the relevant brain regions or networks (31). Thus, increasing our understanding of the neurological underpinnings of PTSD and the neurophysiological effects of NF training in PTSD can have far-reaching implications for the refinement, and success of rt-fMRI NF.

Limitations

Despite the encouraging results, this pilot study has several shortcomings. The major limitation is the very small sample size. The goals were to develop a NF protocol for PTSD patients and to test its feasibility and preliminary promise for treating this highly vulnerable psychiatric population. In line with the pilot nature of the research, there were some irregularities. For example, different approaches were used to define the target region. Also, the number of NF sessions received varied across participants. Moreover, the unblinded design does not allow us to control for placebo or social desirability effects on symptoms ratings. The next phase of research should aim to test the current NF protocol in a standardized, randomized study with a larger sample size.

Furthermore, due to the lack of a control group, it is not possible to exclude that the improvements in PTSD symptomatology are due to factors unconnected to the hypothesized mechanisms of action of NF intervention. Other factors may have contributed to the observed symptom reductions, such as (i) exposure to trauma memories [a large body of evidence suggests that simple exposure to trauma imagery can reduce PTSD symptoms (85, 86)], (ii) placebo effects, (iii) social desirability effects, or (iv) random symptom fluctuations across time. However, prior to this study, all three participants had been exposed to psychological treatments and/or mental-health visits, and all had chronic PTSD symptoms. Thus, exposure to traumatic memories and placebo effects are unlikely to explain the symptom improvements experienced by these patients. Furthermore, the temporal pattern of symptom improvements (time-locked to first NF session) (**Figure 3**) and the changes in rsFC observed (consistent with known neurobiology of PTSD) make the social desirability effect and random symptom fluctuations equally unlikely explanations. In summary, due to the absence of a comparison control group (and the small sample size), no inference can be made about efficacy of the NF intervention for PTSD at this stage. However, the results from this pilot study are promising enough to motivate future investigations into the efficacy of this intervention.

Another limitation is that the patients in this study were not followed clinically after the intervention. Therefore, the persistence of their symptom improvements following NF is unknown. Depending on the persistence of effects, follow-up NF sessions may be needed to maintain improvements. This is an important research direction for future rt-fMRI NF studies.

Finally, this study targeted a very specific subgroup of PTSD patients (i.e., male war veterans with chronic and treatment-resistant PTSD). Thus, it may not be possible to generalize the current findings to other subgroups of PTSD patients [e.g., treatment-naïve individuals, patients with comorbid substance abuse and mood disorders (both very common co-occurring conditions in PTSD), patients with a complex history of trauma,

such as sexual abuse and childhood trauma, etc.]. Nevertheless, war veterans are among the group of PTSD patients who are the least responsive to treatment and show the highest drop-out rates (4). Thus, it is likely that the current rt-fMRI NF protocol may be equally (or even more) feasible and potentially effective among other subgroups of adult PTSD patients.

Conclusion and Final Comments

Unlike other NF methods (such as EEG NF), rt-fMRI NF represents a unique opportunity for targeting specific and deep brain regions involved in the pathophysiology of PTSD. Thus, rt-fMRI NF has the potential to facilitate the translation of neuroscientific knowledge of PTSD into clinical practice. Indeed, the preliminary evidence from this study is encouraging as it suggests that rt-fMRI NF (particularly in a trauma exposure context) on chronic PTSD patients is a feasible and promising new intervention. Further investigation is needed to determine efficacy.

AUTHOR CONTRIBUTIONS

All authors (1) made substantial contributions to conception and design, and/or acquisition of data, and/or analysis, and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; and (3) gave final approval of the version to be submitted and any revised version.

ACKNOWLEDGMENTS

We thank Lynette Averill, Lauren Sippel, Ilan Harpaz-Rotem, and the NCPTSD clinical assessment team. We also thank Shelby Monahan for creating the scary movie localizer, and Hedy Sarofin for her technical assistance.

FUNDING

This study was funded by the U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division. Support for the broader research program was also provided by NIMH (R01MH095789; R01MH100068) and the Yale Center for Clinical Investigation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2016.00111

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

HYPOTHESIS AND THEORY
published: 17 June 2016
doi: 10.3389/fpsyt.2016.00107

Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice?

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Diagnosis and individualized treatment of autism spectrum disorder (ASD) represent major problems for contemporary psychiatry. Tackling these problems requires guidance by a pathophysiological theory. In this paper, we consider recent theories that re-conceptualize ASD from a "Bayesian brain" perspective, which posit that the core abnormality of ASD resides in perceptual aberrations due to a disbalance in the precision of prediction errors (sensory noise) relative to the precision of predictions (prior beliefs). This results in percepts that are dominated by sensory inputs and less guided by top-down regularization and shifts the perceptual focus to detailed aspects of the environment with difficulties in extracting meaning. While these Bayesian theories have inspired ongoing empirical studies, their clinical implications have not yet been carved out. Here, we consider how this Bayesian perspective on disease mechanisms in ASD might contribute to improving clinical care for affected individuals. Specifically, we describe a computational strategy, based on generative (e.g., hierarchical Bayesian) models of behavioral and functional neuroimaging data, for establishing diagnostic tests. These tests could provide estimates of specific cognitive processes underlying ASD and delineate pathophysiological mechanisms with concrete treatment targets. Written with a clinical audience in mind, this article outlines how the development of computational diagnostics applicable to behavioral and functional neuroimaging data in routine clinical practice could not only fundamentally alter our concept of ASD but eventually also transform the clinical management of this disorder.

Keywords: autism spectrum disorder, Asperger syndrome, translational research, diagnostic tests, generative modeling, Bayesian inference, Bayesian models, neuroimaging

OPEN ACCESS

Edited by:
Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:
Maria R. Dauvermann, MIT, USA
Nicole Wenderoth, ETH Zurich, Switzerland

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Specialty section:
This article was submitted to Neuroimaging and Stimulation, a section of the journal Frontiers in Psychiatry

Received: *22 January 2016*
Accepted: *03 June 2016*
Published: *17 June 2016*

Citation:
Haker H, Schneebeli M and Stephan KE (2016) Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? Front. Psychiatry 7:107. doi: 10.3389/fpsyt.2016.00107

INTRODUCTION

An important precondition for successful translation of basic scientific theories into clinical applications is the knowledge of the most pressing unresolved problems in clinical practice. The care for affected individuals can only be improved effectively if these priority problems are identified and used to guide the design of scientific studies. In heterogeneous disorders, such as autism spectrum disorder (ASD), cross-sectional comparisons of patients vs. controls may provide coarse contours of some characteristics of the spectrum, but are usually not sufficient to inform changes in clinical practice (1).

In this article, we adopt the clinician's perspective as starting point for outlining how a computational modeling strategy, based on Bayesian theories of ASD (2–4), could inform the development of diagnostic and predictive tests for improving clinical care for individuals with ASD. For the non-clinical reader, we begin with an introduction to the nosology and current clinical management of ASD. For the clinical audience, later sections on computational theories are written in a non-mathematical way and complemented by figures that illustrate basic principles of Bayesian theories.

Features of ASD – A Brief Overview

Nosology

Autism spectrum disorders are developmental disorders of variable severity and heterogeneous phenotypes. Core diagnostic criteria are persistent deficits in social communication and interaction and restricted, repetitive behaviors and interests. Most affected individuals also show altered reactivity to sensory input or unusual interests in sensory aspects of the environment (5, 6) and motor skill deficits or clumsiness (7). The features are present across the life span, but may remain hidden until unmasked by enhanced social demands during development; conversely, they may become less visible in adulthood due to the development of coping strategies. The spectrum ranges from very severe forms – individuals with absent development of verbal language and complete dependence on support – to light expressions of autistic traits that may be masked by learned coping strategies. Generally, there is a smooth transition from pervasive expressions of autistic traits, which cause significant disability and distress to the affected individual, to autistic personality traits that can be regarded as "normal" variations of human personality and do not cause suffering or impairment.

The severe manifestation of ASD, early childhood autism, often co-occurs with intellectual disability and was first described by Leo Kanner in 1943 (8). The term "autism" was introduced to diagnostic classifications in 1976 (ninth revision of the International Classification of Diseases, ICD-9) and 1980 (third revision of the Diagnostic and Statistical Manual of Mental Disorders, DSM-III), respectively. Lighter manifestations were first described by Hans Asperger (9) and introduced to the diagnostic classifications in 1992 (ICD-10) and 1994 (DSM-IV), respectively, as "Asperger syndrome" (10). In contrast to early childhood autism, Asperger syndrome lacks a general retardation in language and is not associated with intellectual disability. Its recognition and introduction to disease classifications triggered a reframing of the earlier category "autism" as "childhood autism."

This historical background explains why, for almost two decades, the psychiatrists' and the public's concept of "autism" was shaped by the severe form. Awareness for lighter manifestations on the spectrum started to grow only slowly after the release of ICD-10 and DSM-IV. Over time, childhood autism and Asperger syndrome were understood as differential expressions on a spectrum with hypothesized similar pathophysiological mechanisms. Accordingly, the latest revision of the DSM (DSM-5) merged them into a single diagnostic category called ASD.

Epidemiology

Interestingly, the prevalence of autistic spectrum disorder has substantially increased between 1990 and 2010, and around 1% of the population is now thought to be affected by ASD (11). This rise can be explained by the expansion of the diagnostic criteria (inclusion of Asperger syndrome) and increased awareness of both the public and professionals, leading to more diagnoses without an increased rate of the disorder *per se* (12, 13).

Etiology

With regard to etiology, epidemiological studies have long pointed to high heritability and a strong genetic contribution to the risk of ASD, finding concordance rates of 60–70% in monozygotic twins and 18–33% in siblings (14, 15). This strong genetic influence has been further elucidated by recent genome-wide analyses of large populations that suggested two different types of genetic contributions to the risk of ASD (16): while some rare *de novo* mutations can be sufficient to convey risk, in other cases, a wide range (>1000) of common single nucleotide variants may interact in conveying the risk for developing ASD (17). Many of the risk genes for ASD, identified so far, appear to impact primarily on synaptic plasticity and alter connectivity of neural circuits (16). This focus on synaptic connectivity is of relevance for the computational theories discussed below; by contrast, it has not yet been translated into specific therapies.

Treatment

Current treatment concepts of ASD include behavioral interventions, psychotherapy, and pharmacological approaches. In children, early behavioral interventions that foster social interaction and speech development (18, 19) are well established and have proven efficacy (20). Adolescents profit from explicit teaching of social skills in groups (21). For adults with ASD, we lack established disorder-specific psychotherapy concepts, so far, that go beyond social skills trainings (22, 23). Available approaches can be divided into psychoeducation (i.e., providing a concept of the disorder and how the individual symptoms relate to it), teaching of coping strategies, and therapy of comorbidities (e.g., depression or anxiety) with currently available options of psychopharmacology and/or psychotherapy. In pharmacotherapy of ASD, the most frequently prescribed and only FDA-approved substance is the dopamine D2 receptor antagonist risperidone (24). This drug has approval for sedation in the presence of aggression or irritability, in ASD. Off-label use of pharmacotherapy mainly rests on the dopaminergic and noradrenergic stimulant, methylphenidate (25). Its effectiveness is mainly documented in the context of comorbid attention-deficit symptoms (26, 27).

Theories

Theories of ASD have either focused on the social symptoms of ASD [e.g., as a deficit of theory of mind (28), reduced social salience (29, 30), or a lack of social motivation (29, 30)] or on peculiarities of autistic perception [e.g., "weak central coherence" (31–33)]. By contrast, there is no universally accepted mechanistic theory so far, which provides a unifying explanation across the entire range of autistic symptomatology.

A candidate theory that might fill this gap is what one might refer to as the "Bayesian brain" perspective on ASD (2–4). This is an umbrella term for several similar theories that conceptualize ASD under a predictive coding or hierarchical inference framework and explain autistic cognition as the consequence of fundamental abnormalities in perception and learning. This computational view on ASD suggests concrete models that can be tested by cognitive and neurophysiological studies and that may provide a fundament for developing clinically useful tests. This is the topic of this paper.

Contemporary Challenges in Clinical Care for ASD

The present clinical management of ASD is not satisfactory in several regards. In the following, we outline some key challenges in diagnosis and treatment of children and adults along the autism spectrum, where we see particular opportunities for Bayesian theories to contribute to improvements.

Diagnostic Challenges

Today's diagnostic criteria defined in ICD and DSM and respective diagnostic procedures were derived from Kanner's and Asperger's descriptions of the behavior and development of affected young boys (8, 9). Factors that cause heterogeneity in developmental trajectories of affected individuals and, therefore, observable manifestations of ASD are the degree of severity, the absence or presence of spoken language, gender, age, intelligence, and the individual history of life experience and learning (spontaneous or fostered by training). This heterogeneity causes problems in the diagnosis of ASD.

Since mechanistic definitions and measures of ASD are lacking, diagnosis rests, as for all psychiatric disorders, on symptoms and signs and the developmental history. The Autism Diagnostic Observation Schedule (ADOS) has been developed as a semi-structured assessment tool to standardize clinical examination of the diagnostic criteria of ICD-10 and DSM-IV (34). In combination with the Autism Diagnostic Interview (revised version, ADI-R) (35), which is conducted with parents or caregivers of affected children, it is regarded as gold standard of ASD diagnosis, particularly for children at the more severe end of the spectrum (36). This, however, directly leads us to the first clinical challenge: (*i*) ADOS and ADI-R are time-consuming procedures, which rely on the availability of specifically trained and experienced clinicians. It would be extremely desirable to have a quicker, easier, and less resource-demanding diagnostic test, which could be applied by non-specialized professionals. This would considerably facilitate early diagnosis, which, in turn, is essential for the success of therapeutic (behavioral) interventions at an early stage.

Autism Diagnostic Observation Schedule and ADI-R have less sensitivity in children and adults with higher functioning and milder forms of ASD. This is a result of the greater variance in observable symptoms in these individuals, e.g., due to acquisition of coping strategies (37). In individuals at the lighter end of the spectrum, symptoms may be covered in childhood, until social demands exceed available coping strategies. Later in development, symptoms may become masked by acquired strategies that facilitate social interaction and communication. This variability renders the diagnosis of children, and particularly adults, at the milder end of the spectrum, challenging. Even if these highly functional individuals may show few classical autistic symptoms at first sight, their ability to cope with complex environments and daily demands can be frail. This causes significant exhaustion and suffering, and promotes comorbidities, e.g., depression, anxiety, or substance abuse (38).

The diagnosis of individuals at the lighter end of the spectrum, therefore, requires the detection of subtle signs. For example, peculiarities in social interaction and communication become apparent only in deeper interactions and/or over longer periods of observation. The repetitive nature of behavior manifests itself on larger temporal or spatial scales than in children. Reliable diagnosis often requires an extensive exploration of the patient's way of perceiving and understanding the world, themselves, and others. Such diagnostic exploration can be instructive in adult ASD patients with a high degree of socioemotional development, who have established a concept of their differences to others. However, compared to non-developmental psychiatric disorders, two complications frequently arise. First, for the patient, his/her autistic symptoms have always been present, and there is no non-affected state to which a comparison could be established. Second, the establishment of abstract representations of the (autistic) self and (non-autistic) others is a core problem in ASD and renders the recognition and description of one's own particularity difficult.

Another difficulty of recognizing ASD arises in this same group of less severely affected individuals by the fact that, at first clinical contact, their autistic symptoms are often overshadowed by acute exacerbation of secondary effects or comorbidities, such as depression, which often represent their main motivation for seeking clinical help (39–41).

Taken together, a second challenge is the (*ii*) diagnosis of mild forms of ASD due to the great variance of presented symptoms and the difficulty in exploring the inner world of an autistic mind in the absence of quantitative tools. Experienced clinicians, who are able to detect these mild forms of ASD by clinical examination, are even rarer than experts in ADOS/ADI-R. This is because awareness of the lighter forms of ASD has grown only slowly, especially in adult psychiatry, where many older patients remain misdiagnosed because they entered clinical care before the introduction of the diagnostic classification of Asperger syndrome in the 1990s (42, 43).

A third challenge is the (*iii*) detection of very young children at risk, such as siblings of already diagnosed children. Their genetically increased risk for ASD makes them candidates for screening and early intervention in order to optimize their long-term outcome (15). The diagnosis in these very young infant siblings is based on close monitoring of behavioral development (44), but complicated by various onset patterns and the limited repertoire of observable behavior at this early developmental stage (45). Eye tracking of visual scanning patterns is a potentially promising marker of altered cognition at this early stage (46), but remains to be validated in prospective studies.

A fourth diagnostic challenge concerns (*iv*) the assessment of intelligence in ASD patients without spoken language at the

severe end of the spectrum. There is evidence that the degree of intellectual disability in ASD individuals with no verbal communication skills is overestimated (47), with possibly severe consequences for the patient. Again, objective and quantitative assessment tools are lacking so far.

In summary, so far, appropriate diagnostic procedures are available only for a limited group of ASD patients with specific degrees of severity and age. Furthermore, their reliance on specific expertise and training makes it difficult for the average psychiatrist to achieve reliable clinical diagnoses of ASD.

Treatment Challenges – Behavioral Therapy and Psychotherapy

As described above, several effective concepts of early behavioral intervention and social skills training are established for children across the whole spectrum. By contrast, the follow-up treatment in adulthood still poses considerable problems. This brings us to further concrete challenges:

(*v*) So far, there are no concepts of behavioral interventions that foster socioemotional development of severely affected individuals in adulthood, especially not for those without spoken language and possibly underestimated intelligence (48).

(*vi*) For the mild end of the spectrum, some first concepts of social training for adults do exist (23, 49, 50). However, treatment concepts focusing on "hidden" autistic symptoms in adults, such as sensory oversensitivity, detail-dominated perception, or the need for structure and rituals in self-organization are still to be developed (51).

(*vii*) There is a lack of concepts how the psychotherapy of comorbid disorders, such as depression, needs to be adjusted in the specific context of ASD (52).

Treatment Challenges – Pharmacotherapy

(*viii*) There is a complete lack of pharmacological therapies that are motivated by concrete pathophysiological theories and influence either the neurodevelopment in children or tackle the mechanisms behind autistic symptoms in adolescents and adults (53, 54). This lack is remarkable, given that ASD is now considered to represent one of the most strongly heritable and, therefore, biologically determined psychiatric disorders (11, 55).

(*ix*) Trial and error psychopharmacological approaches show some beneficial effect in individual patients. An individualized prediction of treatment response could save time and prevent patients' suffering from unnecessary side effects of ineffective medication attempts.

A COMPUTATIONAL FRAMEWORK FOR ASD

Computational Approaches to Psychiatric Disorders

Addressing the clinical challenges highlighted above represents a daunting problem. Without a fundamental mechanistic explanation for the manifold clinical manifestations of ASD, we lack a fundament for developing diagnostic tests and new treatment strategies. Clearly, this situation is not unique to ASD: psychiatry generally lacks mechanistically grounded diagnostic tests. In contrast to other areas of medicine where hidden disease mechanisms can often be inferred by advanced measurements of downstream consequences (e.g., biochemical or immunological assays of blood samples), the diagnosis of psychiatric disorders is hampered by lack of access to disease-relevant tissue (i.e., the brain) and the absence of biochemical or genetic markers with predictive utility (56, 57). Similarly, while structural neuroimaging techniques are used in clinical practice to rule out non-psychiatric disorders ("organic" causes), their functional counterparts are remote from neuronal processes of interest, e.g., neuromodulatory signals. More than two decades of functional neuroimaging research have yielded no application that has entered routine psychiatric practice so far (1, 58).

A potential alternative to classical neuroimaging is offered by emerging computational methods based on generative models of measurable behavior or brain activity (59). Generative models are forward models that describe how latent (hidden) cognitive or physiological processes x could have generated experimentally measured data y (**Figure 1**). Based on Bayes' theorem (60), generative models allow for solving the inverse problem of inferring the hidden processes from empirical data, yielding the posterior probability $p(x|y)$ of the hidden cause of interest. This computational approach allows one to compute subject-specific parameters that determine the hidden neuronal or cognitive states of a circuit. Furthermore, the plausibility of different generative models can be evaluated using statistical model comparison techniques (61, 62).

In the context of psychiatric disorders, the relatively straightforward availability of behavioral or brain activity measurements suggests that validated generative models could be developed into clinically applicable "computational assays," in analogy to biochemical assays in internal medicine (63). A series of recent proof of concept studies (64–66) have been an important stimulant for the development of the emerging field of computational psychiatry (59, 67–69).

The "Bayesian Brain"

Overall View

Bayesian inference is remarkably analogous to perception, where the challenge is to distil meaning from noisy and ambiguous sensory inputs. Based on the principles of probability theory, Bayesian interpretations of cognition refer to "beliefs" as

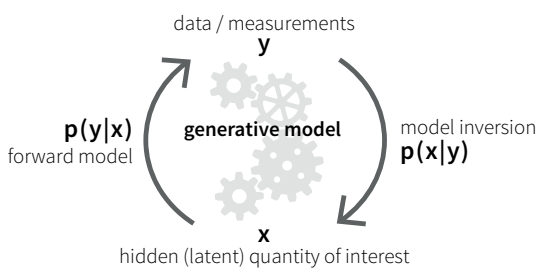

FIGURE 1 | Schematic of the principles of a generative model.

probability distributions (i.e., a probabilistic representation of a particular state of the world) and how these beliefs are updated in the light of experience (observed data). Bayes' theorem describes how the observation of new data (likelihood) changes a prior belief into a posterior belief. This posterior belief represents the inference about the most likely cause behind the observed data, given the previous knowledge, and becomes the new prior belief or prediction for future observations (see **Figure 2**).

We refer to a Bayesian perspective on cognition as the "Bayesian brain hypothesis," an umbrella term for several related concepts (70–73). All of them regard the brain as an inference machine, resting on a generative model of sensory inputs, which are caused by states of the environment. For simplicity, we will often refer to this generative model of sensory inputs as the brain's internal model of the external world. By inverting its generative model, the brain can infer the most likely environmental state (cause), given the sensory inputs it has received. Furthermore, the brain can use its internal model for prediction and compute the probability of certain environmental states arising from chosen actions (74).

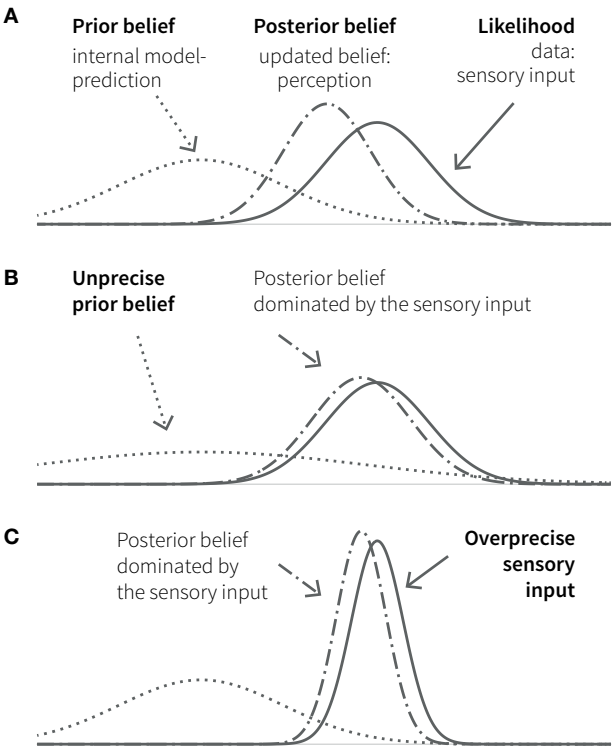

FIGURE 2 | **Principles of Bayesian inference**. **(A)** A prior belief (knowledge, expectation, or prediction; dotted line) is combined with the likelihood (observed data, e.g., sensory input; solid line) in the form of Gaussian probability distributions. The width of the curves represents uncertainty (variance); its inverse (the narrowness of the curve) represents the precision of or the confidence in the respective belief or data. The resulting posterior belief (dashed-dotted line) represents the updated belief, as a precision-weighted compromise between prior and likelihood, which is dominated by the quantity with higher precision. In cognition, perception can be understood as the formation of a posterior belief in response to sensory input. The lower panels show two additional situations, in which the posterior (perception) is biased toward the (sensory) data: in one case because the prior (belief) is unprecise **(B)**; in the other, because the (sensory) data are over-precise **(C)**.

This Bayesian interpretation of perception has become a widely used perspective and has enabled the understanding of many perceptual phenomena, including a unification of perceptual laws (75), multisensory integration (76, 77), and the nature of sensory illusions (78).

Learning

The brain's internal model can be updated over time; this corresponds to learning and rests on a key quantity, the prediction error. This is the difference between the predicted and the actual sensory input and constitutes part of an approximation to surprise (**Figure 3A**) (72). An influential recent hypothesis – the so-called "free-energy principle" (79, 80) – is that perception and action selection are governed by one overarching objective: the minimization of surprise and hence the avoidance of prediction errors. The free-energy principle essentially views the Bayesian brain as implementing a homeostatic principle of information processing where the absence of prediction error represents the set point against which actions are chosen.

In principle, there are two ways of minimizing prediction errors. First, a prediction might be fulfilled by choosing the appropriate action. This includes moving one's sensors (e.g., eyes, limbs, or the entire body) to parts of the environment where the sensory inputs better match the predictions (**Figure 3B**). Second, the brain can use surprise as teaching signal to adjust its beliefs. This corresponds to learning or updating its generative model, so that the current prediction error is explained away and more accurate future predictions become possible (**Figure 3C**).

Uncertainty

Importantly, however, not all unpredicted inputs are equally informative. Due to stochasticity in the environment and noise inherent to all sensory organs, not all prediction errors signal true changes in learnable regularities. Given this uncertainty, updating the generative model in response to each and every input could result in overfitting, i.e., an overly precise and brittle model with limited generalizability over time. Instead, belief updates should be governed by the balance between two quantities: the uncertainty about the sensory input (i.e., expected signal-to-noise ratio), and the uncertainty of the prior belief. For a wide range of learning models, this can be described by an iconic equation (Eq. 1). That is, any change in belief is proportional to prediction error, but weighted by the ratio of the precision of the sensory input and the precision of the prior belief (81).

$$\Delta\text{belief} \propto \frac{\text{precision}_{\text{input}}}{\text{precision}_{\text{prior belief}}} \times \text{prediction error} \qquad (1)$$

This precision ratio can be regarded as dynamic learning rate: it is high whenever the confidence in the sensory input (bottom-up information) is higher than the confidence in the current belief (top-down predictions of the model), or conversely, when the uncertainty of the predictions provided by the internal model is higher than the uncertainty about the sensory input. The higher

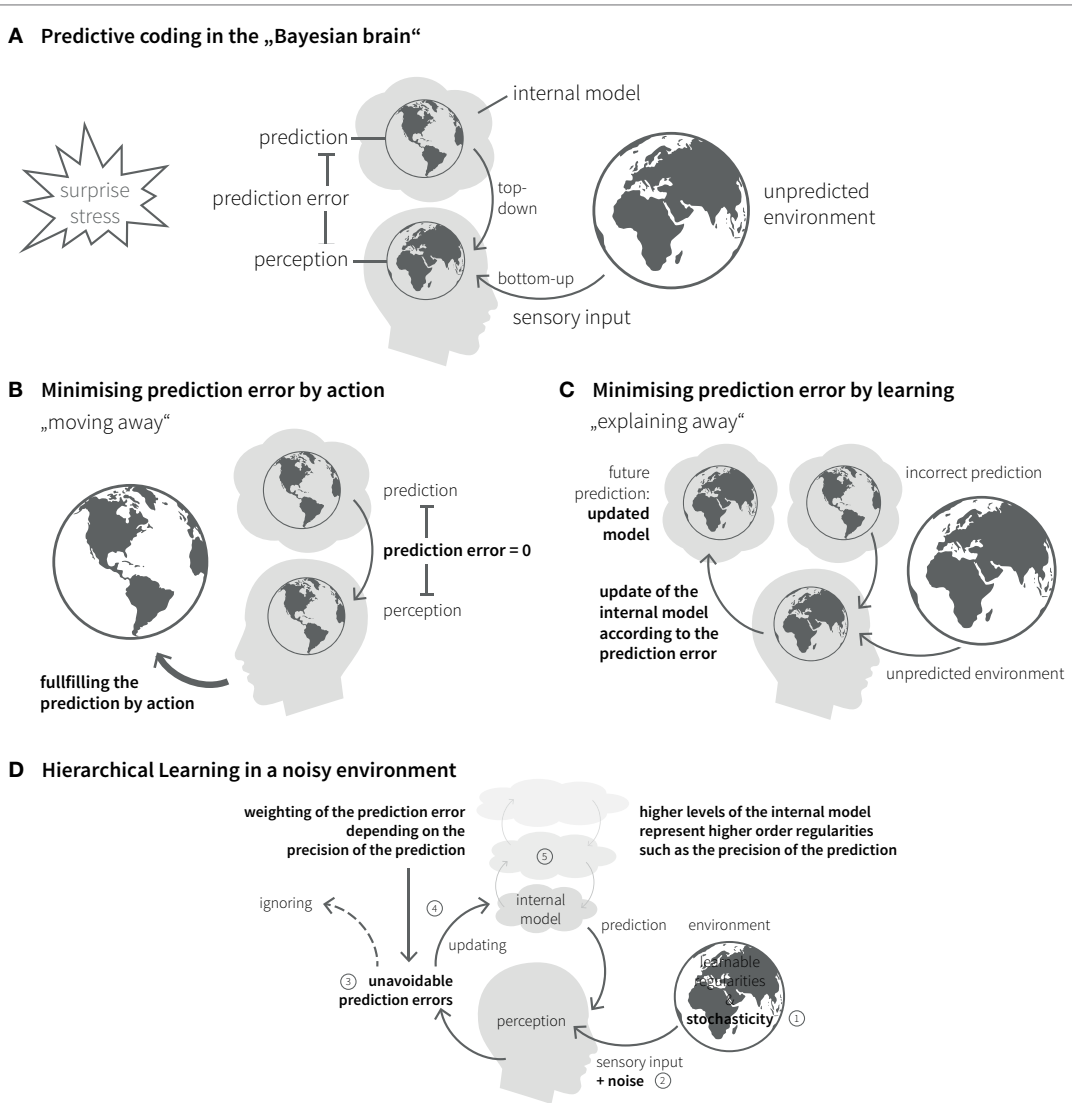

FIGURE 3 | **Bayesian inference in the brain**. **(A)** The "Bayesian brain" predicts (based on its internal model) the incoming sensory input from the environment and compares it with the actual input. The difference between prediction and sensory input is called prediction error. The brain's homeostatic goal is to minimize prediction errors. Prediction errors can be reduced in two ways: action or learning. **(B)** Predictions can be fulfilled by choosing actions that lead to expected sensory inputs. **(C)** Incorrect predictions can be adapted according to prediction error. Under this model update (learning), the prediction error is explained away. **(D)** Due to stochasticity in the environment (1) and noise of sensory channels (2), prediction errors can usually not be explained away completely (3). Their impact on belief updates depends on the relative precision of sensory input and prediction (4), which is coded in higher levels of the internal model (5).

this precision ratio, the more informative surprising input and the more pronounced the updating of the internal model.

Cognitive Hierarchies

The causal structure of the world, with its nested spatial and temporal scales, implies that the brain's internal model also possesses a hierarchical structure, which is a natural form for Bayesian inference: hierarchical models allow to encode information about the precision of beliefs at one level by values of hierarchically higher levels (81–83) (**Figure 3D**). In a hierarchical setting, information passes from sensory cortical areas to update higher levels within the cortical hierarchy, representing more and more abstract information on higher temporal and spatial scales [cf. (84)]. The more precise these abstract representations are established, the less impact any surprising experience has on revising the established internal model. In other words, more precise high-level beliefs exert stronger guidance in interpreting new experiences and shield against continuous reshaping of the brain's model of the external world.

Homeostasis and Psychopathology

Theories like predictive coding or the free-energy principle are theories of cognitive homeostasis: they describe how a system responds adaptively to a mismatch between desired (predicted)

inputs and actual inputs. A mismatch (prediction error, surprise) represents a stressor to the cognitive system and triggers adaptive responses, such as the change of internal settings (update of beliefs) or outputs (motor actions). In the context of predictive coding, the adaptive updating of internal beliefs is also referred to as "explaining away" prediction errors. An acute or chronic impairment in explaining-away prediction errors represents a form of "cognitive stress" and will be registered by higher model levels on the cognitive hierarchy involved in monitoring the cognitive performance of the lower levels of the internal model (85).

Since the majority of current computational concepts of psychiatric disorders regard aberrant learning and inference as core components of maladaptive cognition (59), the three elements in Eq. 1 – prediction, prediction error, and precision – offer an interesting perspective for clinicians. They suggest that cognitive stress due to maladaptive inference arises from alterations in one or several of these three core components. These quantities span a three-dimensional space where different pathologies could be located (86). This means that similar psychopathological phenotypes (based on disturbances of Bayesian inference) could arise by several pathomechanisms, affecting differentially the biological basis of one or more of these computational quantities.

Individual differences in the structure of internal models or model parameters represent specific cognitive styles or cognitive strategies and would manifest in behavioral differences. Provided one has generative models that can infer, from subject-specific behavior, on the structure and parameterization of an individual brain's generative model, powerful diagnostic tests might become possible. Such computational assays – which correspond to generative models of generative models – would become particularly powerful, if mappings between the above computational quantities and specific neurophysiological entities could be established.

A "Bayesian Brain" Perspective on ASD

A Clinician's View as Starting Point

Autism spectrum disorder is clinically characterized by prominent perceptual aberrations, which appear to map naturally on impairments of hierarchical Bayesian inference. Individuals with ASD have striking difficulties in distinguishing between relevant (informative) details and irrelevant, random changes. For example, during the interaction with another person, a patient with ASD may direct more attention to a new haircut or the color of the shirt than to the emotional expression of the other's face. Furthermore, ASD patients struggle to establish generalizable, abstract representations by making meaningful connections and tend to have overly precise representations of single observations and detailed sensory aspects. For example, they take expressions too literally, or do not know how to behave in situations that only subtly differ from known constellations; small details, e.g., variations in location or timing, can be sufficient to induce feelings of uncertainty and lack of control. Finally, they experience a chronic sensation of being unprepared for whatever happens, unless they can exert control (and thus avoid surprise) in a stable, well-known environment. This may underlie their desire for fixed rituals, such as never changing the exact order of a sequence of actions in everyday life.

Summary of Current Theories

Several recent articles have suggested that aberrant Bayesian inference underlies perceptual abnormalities in ASD. For example, Pellicano and Burr (2) proposed that ASD is characterized by overly flat priors, which lead to percepts dominated by the sensory input. Their proposal was extended by Lawson et al. (3), who pointed out that the precision of top-down predictions need to be weighed against the expected precision of bottom-up sensory input (**Figure 2C**; compare Eq. 1). They highlighted the importance of postsynaptic gain control as a potential neurobiological mechanism for precision weighting and hypothesized that GABA, acetylcholine, and oxytocin could play a central role in the adjustment of precisions at different hierarchical levels. Finally, Van de Cruys et al. (4) pointed out that normal, or even tight, high-order beliefs could be present in ASD, provided that their effects are outweighed by overly high precision of sensory prediction errors. Again, this speaks to the crucial role of precision ratios (see Eq. 1) for dynamically governing belief updates across hierarchical levels.

Autistic Perception

Impairments of hierarchical Bayesian inference provide an explanation for the different clinical symptoms described above. Specifically, aberrant updating of the internal model due to overestimating the precision of bottom-up sensory input in relation to the precision of top-down predictions (see **Figures 2B,C** and Eq. 1) would lead to a perceptual style, which is dominated by detailed but irrelevant aspects of the environment and a difficulty in establishing stable and precise representations of abstract quantities at high levels of the perceptual hierarchy (**Figure 4A**). Interestingly, this suggests a concrete computational mechanism for the long-standing concept of "weak central coherence," which postulates that processing of local details dominates perception in ASD, at the expense of global integration of information (31, 32). The overweighting of uninformative sensory prediction errors leads to constant fluctuations and large uncertainty at higher levels in the generative model, which represent overarching, abstract concepts. Additionally, a relative failure of encoding or updating high-level precision implies that even relatively predictable stimuli will be perceived as continuously surprising. Overall, the proposed dysbalance in low- vs. high-level precisions result in an overfitted model that is dominated by sensory details and has limited generalizability.

Autistic (Inter-)Action

Our inner representation of the world not only explains what we perceive but also guides our interactions with the world. Models that concentrate on detailed aspects of the sensory world (i.e., overly high precision of sensory prediction errors) elicit actions that serve to explain away these prediction errors (such as seen in precisely defined autistic rituals, **Figure 4B**). Importantly, this interferes with adaptive actions in the presence of irrelevant changes in details. This difficulty of establishing and applying

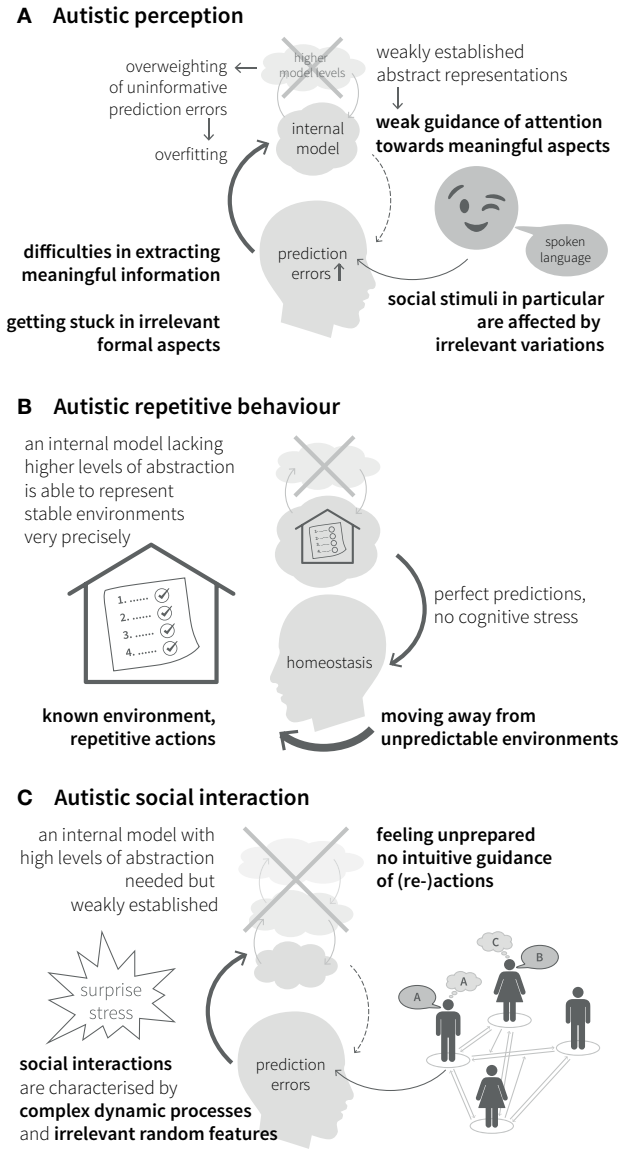

FIGURE 4 | Autistic symptoms from a Bayesian viewpoint. (A) *Perception*. Weakly established abstract representations provide predictions with low precision and fail in guiding attention toward informative stimuli. Especially for complex stimuli with frequent irrelevant variations, such as social stimuli, attention can be attracted by unpredicted changes in irrelevant formal aspects. Overweighted low-level prediction errors, due to overly high sensory precision, cause overfitting of the internal model and difficulties in extracting meaningful information. This impairs the establishment of high-level (abstract) representations and reduces the ability to explain away future prediction errors. **(B)** *Behavior*. Minimization of prediction errors is achieved more easily by moving away from unpredictable environments into highly regular environments with repetitive actions and rituals, since they can be precisely predicted by a model without many levels of abstraction. **(C)** *Interaction*. Social interactions in particular are characterized by complex dynamic processes and irrelevant random features, which require regularization and suppression by an internal model with a high degree of abstraction and precise predictions. A relative lack of this model makes it difficult to infer the causes of social stimuli (i.e., understand the meaning of social processes) and, thus, to interact with others.

abstract representations to interpret sensory inputs and guide action causes greatest difficulties in highly unpredictable environments, such as completely novel situations or social interactions, which are particularly dynamic and ambiguous (noisy) (**Figure 4C**). Similar problems can be expected in areas, where highly abstract contents are exchanged, like in human communication. Hence, the Bayesian perspective offers an intuitive explanation for the theory of mind deficits in ASD. From this point of view, ASD can be seen as a general disorder of hierarchical inference that manifests most prominently in the social domain without being limited to it.

The Spectrum Nature

Autism spectrum disorder shows pronounced heterogeneity, both with respect to the behavioral phenotype and severity of impairments. The hypothesized fundamental mechanism affected in ASD, hierarchical Bayesian learning, is based on three main pillars: predictions, prediction errors, and the respective precisions. As indicated above, these three variables span an explanatory space of the potential computational pathomechanisms that could underlie impairments in hierarchical Bayesian learning. For example, predictions and/or prediction errors could be incorrectly calculated at the level of specific neurons (e.g., abnormal integration of dendritic inputs to supragranular pyramidal cells), or they could be conveyed incorrectly to target neurons (e.g., presynaptic or postsynaptic deficiencies of long-range connections). Alternatively, as suggested by Lawson et al. (3) and Van de Cruys et al. (4), precisions could be tuned abnormally. This could arise, for example, from a dysregulation of neuromodulatory transmitters (e.g., dopamine, acetylcholine, noradrenaline), which affect postsynaptic gain by modulating calcium-dependent potassium channels. Due to the anatomy of their specific projection pathways, the individual neuromodulators (and their potential dysregulation) impact differentially on different cortical areas (e.g., affecting different sensory modalities and different levels of the cognitive hierarchy).

This list of possibilities is not exhaustive, but illustrates how the phenotypic and clinical variability of ASD patients could arise from different impairments of hierarchical Bayesian inference. In other words, different autistic phenotypes could arise from different impairments in the computation of key variables, such as precisions or prediction errors. The present framework, thus, offers a broad range of explanations, how the spectral nature of ASD – in severity and phenotype – could arise, and suggests possibilities to disentangle potential mechanistically different subtypes of the disorder.

Developmental Trajectories

Bayesian theories of ASD also provide an explanation for the spectrum of developmental trajectories and how they are influenced by the history of life experience and learning. The hypothesis that ASD is characterized by an inflated ratio of the precision of bottom-up sensory input in relation to the precision of top-down predictions (Eq. 1) makes concrete predictions about the learning conditions under which ASD patients can benefit. These conditions match precisely the conditions to which

behavioral therapy for children with ASD has converged over the years (20): a well-known environment that causes little surprise and offers new inputs with little noise (unexplainable variability) across many repetitions. According to the therapeutic experience of the authors, new actions are best learned by step-by-step instruction (as opposed to mere observation), and abstract concepts are easiest learned through explicit definition (rather than by intuitive buildup) (21). If such conditions are present and an affected individual is exposed to enough inputs over a longer time, a sufficiently rich representation of the world and successful behavioral strategies can be learned. Variations in the occurrence of these conditions in different domains or stages of life could explain the evolution of symptoms over time in form of developmental steps and functional adjustment through training.

Comorbidities

Comorbidities occur frequently and can impede this progress of adjustment. The most frequent and relevant ones are stress-related disorders, such as depression or anxiety (87). From the Bayesian brain perspective, these can be interpreted as a consequence of chronically elevated cognitive stress levels in individuals with ASD, which originates from their impaired ability to explain away prediction errors. As alluded to above, a persistent impairment of minimizing prediction errors in a specific processing stream is likely registered by higher systems for self-monitoring (85) and creates the continuing experience of an unpredictable environment of bewildering complexity. This may engender to the meta-cognitive evaluation that the brain's model of the world is inadequate to deal with its complexity, leading to estimates of low self-efficacy (88) and a pervasive feeling of vulnerability (Stephan et al., In preparation[1]). This, in turn, may constitute a fundament for the development of comorbidities like depression and anxiety in ASD.

Similarities with Schizophrenia

It is of interest to note that similar Bayesian theories have previously been stated in the context of schizophrenia (63, 68, 89–92). ASD and schizophrenia exhibit some striking similarities in certain symptoms. In fact, the term "autism" was introduced by Bleuler when referring to symptoms like social withdrawal in schizophrenia (93). Perceptual aberrations, e.g., a reduced tendency to illusions (75), take a similar form in both disorders, suggesting that similar impairments in Bayesian inference may be present in both disorders. However, the markedly different age of onset of the two disorders requires an explanation why a common mechanism, such as aberrant belief precisions, may reach a critical threshold at different times during development. One might speculate that this results from epigenetic differences in the two disorders, i.e., differential interactions of genetic predispositions with environmental influences. Also, salient symptoms as the presence of positive symptoms in schizophrenia deserve attention (94). Notably, psychotic episodes are not uncommon in adolescents with ASD, although they are mostly shorter in duration and present less well-established delusions than in schizophrenia (10, 38, 95). Furthermore, neurobiologically, ASD and schizophrenia share putative risk genes (96) and may involve analogous abnormalities in the neuromodulatory regulation of postsynaptic gain, as described further below (3, 92).

[1]Stephan KE, Manjaly ZM, Weber L, Paliwal S, Mathys C, Gard T, et al. From dyshomeostasis to fatigue and depression – a Bayesian account of metacognition and self-efficacy. (In preparation).

CONSIDERATIONS FOR FUTURE STUDIES

Present Empirical Findings

The recently developed Bayesian brain theories of ASD can not only explain cardinal features of autistic symptomatology but also a broad range of previous empirical findings in the domain of neuropsychology, neurophysiology, and functional neuroimaging. A comprehensive overview of these interpretations goes beyond the scope of this article, but can be found in several recent articles on Bayesian brain theories of ASD (2–4).

In the elaboration of the Bayesian brain hypothesis of ASD (2) and subsequent theoretical papers (3, 4, 97–99), results from numerous earlier cognitive and psychophysical studies were reinterpreted *post hoc* in the novel framework. So far, only a few subsequent experimental studies in individuals with ASD were designed *a priori* to test the predictions of the Bayesian brain hypothesis. For example, a psychophysical study by Palmer et al. (100) showed that adults with ASD exhibited the typical perceptual effects of the rubber hand illusion but showed reduced influence of the illusion on subsequent grasp movements. This result speaks against a general insusceptibility of ASD individuals to the illusion and is better explained by a stronger weighting (precision) of proprioceptive sensory input relative to reliance on prior context information. Another psychophysical study demonstrated decreased loudness adaptation in adults with ASD, in accordance with the notion that a failure of updating precision of beliefs (predictions) slows down surprise reduction during a series of predictable stimuli (101). Similarly, an EEG study using a mismatch negativity design which showed that, compared to unaffected participants, children with ASD display a diminished top-down P300 amplitude for unexpected stimuli and a greater amplitude for expected stimuli. Again, both results are compatible with a reduction in the precision of predictions (priors) in autistic patients compared to healthy subjects (102). Finally, a behavioral study of adults with ASD showed reduced learning performance in a volatile compared to a stable environment, consistent with the proposed inability to establish stable high-level representations of abstract rules (103).

These emerging empirical findings speak to the utility of the Bayesian brain perspective for understanding aberrant computation and pathophysiology in ASD. However, a direct link to clinical challenges and practice has been missing so far.

Modeling Cognition

Bayesian brain theories can be implemented by a variety of different models (72, 104). These typically take a hierarchical form where messages are exchanged bottom-up and top-down between layers, resembling the architecture of the cortex with its hierarchically organized connections (105). One well-known hierarchical Bayesian model is predictive coding (72, 106), which

posits that each information processing level (e.g., cortical area) predicts the activity in the next lower level of the hierarchy and sends this prediction via top-down or backward connections. The lower level computes a prediction error (the difference between its actual and the predicted activity), weighted by the precision of the prediction, and returns this precision-weighted prediction error by bottom-up or forward connections to the higher level where it serves to update the prediction. This process takes place across all hierarchical levels until prediction errors are minimized throughout the entire hierarchy.

This model, and variants thereof, has already found widespread application to other psychiatric disorders with perceptual aberrations, in particular schizophrenia (63, 89, 90, 92, 107). Notably, it contains the three main building blocks of inference mentioned above (predictions, prediction errors, and precision), each of which has some putative physiological counterparts. For example, prediction error signaling in cortex likely rests on fast glutamatergic transmission, probably involving fast AMPA receptors under regulation by slower NMDA receptors (91, 108); predictions are probably conveyed by glutamatergic backward connections and exclusively via slow NMDA receptors (72, 91); finally, precision, which is essential for the context-dependent weighting of prediction errors, may be regulated by neuromodulators (dopamine, acetylcholine, noradrenalin, etc.) and local GABAergic interneuron activity, both of which modulate the gain of the postsynaptic neuron (92).

Predictive coding is a model of inference and does not directly account for across-trial learning. A hierarchical Bayesian model that shares key features with predictive coding but focuses on learning under the influence of different forms of uncertainty is the Hierarchical Gaussian Filter (HGF) (81, 109). Using a variational approximation, it derives analytical update equations with subject-specific parameters that encode an individual's approximation to ideal Bayesian learning. The HGF can be applied in a meta-Bayesian way, with an examiner (e.g., psychiatrist) using Bayesian inference, to infer on Bayesian inference processes that underlie the observed behavior of a patient (110).

The HGF is particularly suitable for complex probabilistic learning tasks, whose statistical structure is volatile. Its hierarchical structure captures the relations of coupled quantities in the world, such as how sensory inputs depend on probabilistic associations (contingencies) which, in turn, evolve as a function of environmental volatility. Each of these quantities evolves as a Gaussian random walk, with its precision determined by the level above, and belief updates are governed by precision-weighted prediction errors as shown by Eq. 1. This formulation has found successful application in several recent studies with healthy participants, showing that the HGF explains learning and decision-making under volatility better than other commonly used models (111–113). Associative learning tasks that include phases of volatility (i.e., weakening or reversal of previously learned associations) represent attractive paradigms to study potential peculiarities in hierarchical inference in individuals with ASD, since their problems in establishing abstract high-level representations arise mainly in contexts with either high levels of sensory noise (where increased precision of bottom-up signaling is detrimental) or temporal uncertainty (where weak top-down predictions are further diminished by volatility).

Modeling Neurophysiology

The Bayesian brain perspective is an attractive framework for understanding pathophysiology in ASD. In principle, one could imagine that carefully designed behavioral tasks alone could support model-based diagnostics and predictions. However, the utility of the Bayesian brain perspective extends beyond modeling cognition. In particular, generative models of behavior can finesse analyses of functional neuroimaging data and allow to identify potential neurophysiological fundaments of computational processes. For example, trial-by-trial estimates of computational quantities, such as prediction errors or precisions, can be used as parametric modulators in a general linear model (GLM) of fMRI data, an approach commonly referred to as "model-based fMRI" (114). This approach has been used, for example, to identify links between activity in neuromodulatory nuclei and computational trajectories, such as (precision-weighted) prediction errors or uncertainty (111, 115–117). For example, Iglesias et al. (111) showed that low-level precision-weighted prediction errors about visual stimulus outcome were reflected by fMRI activity in the dopaminergic midbrain, whereas high-level prediction errors about stimulus probabilities were encoded in the cholinergic basal forebrain.

Establishing computational neuroimaging probes of neuromodulation is a theme of general importance in computational psychiatry, since this may provide a physiologically interpretable stratification of patients from spectrum disorders with direct implications for individual treatment (118). In the context of ASD, a dysregulation of neuromodulatory mechanisms could underlie abnormal precision-weighting of prediction errors (and the ensuing behavioral consequences) in a subgroup of patients. While group-level abnormalities of serotonergic and dopaminergic transporter activity have been reported by previous studies using single-photon emission computed tomography and positron emission tomography in individuals with ASD (119, 120), the results are mixed, presumably due to the spectrum nature of ASD. This likely pathophysiological heterogeneity is also reflected by the highly variable response of ASD patients to a variety of commonly used psychiatric drugs, which affect neuromodulatory transmitters, including antipsychotics and stimulants (121, 122). Individualizing pharmacotherapy would require a non-invasive and easily applicable assay of neuromodulatory function in individual patients. Developing such assays on the basis of generative models of behavior and computational functional neuroimaging represents a central goal for model-based diagnostics in ASD.

In addition to model-based fMRI investigations that are supported by modeling of behavior, the Bayesian brain perspective on ASD also makes predictions about neurophysiology that can be examined on their own, without reference to behavior. Most importantly, as alluded to above, the form of hierarchical Bayesian models such as predictive coding, with their emphasis on exchange of predictions and prediction errors across hierarchical levels, shows a remarkable correspondence to structural and functional principles of the cortex (72). That is, sensory processing streams in cortex, such as the visual, auditory, or somatosensory system, are characterized by a hierarchical structure that rests on interregional forward (bottom-up) and backward (top-down) connections with laminar and functional specificity (123–125).

Numerous neurophysiological studies have provided evidence for signaling of prediction errors along forward connections and predictions along backward connections [(63, 72) for reviews see (126, 127)]. As a consequence, a putative pathophysiological mechanism that alters the signaling of predictions or prediction errors, respectively – either on their own or by abnormal precision-weighting – should be expressed in selective changes of forward or backward connections in a particular sensory hierarchy. This implies an important role for models that can infer changes in these connections from functional neuroimaging data.

A generative modeling framework, which is capable of differential inferences about forward and backward connections, is dynamic causal modeling (DCM). This approach has been implemented for a range of measurements, including fMRI (128) and EEG (129). DCM of fMRI represents a generative model of local BOLD signals in a distributed set of regions, describing how the measured fMRI signals arise from net population activity of large populations of neurons that communicate via synaptic connections (128). Inverting this model allows for estimating the strengths of directed synaptic connections between regions, thus moving beyond purely correlational statements about network architecture as obtained by functional connectivity analyses.

Dynamic causal modeling is beginning to find widespread use in psychiatry. In the context of schizophrenia, several studies have been conducted in individuals at risk (130, 131) and in patients during the first episode (132), early course (133), or chronic state of schizophrenia (134). These studies demonstrated differences in functional network architecture and effective connectivity compared to healthy controls across various tasks. More recently, DCM studies have been conducted in individuals with ASD. Radulescu et al. (135) examined connectivity during a verbal fluency task and found that adults with ASD relied more strongly on bottom-up connections, compared to dominance of top-down connections in the control group. Gu et al. (136) used DCM to infer connection strengths between the extrastriate body area, the anterior insular cortex, and the lateral prefrontal cortex during an empathy for pain task. They found a greater disinhibition in the anterior insula in a group of high-functioning adults with ASD compared to a control group. In brief, the results of DCM studies in both schizophrenia and the ASD point to dysconnectivity of cortical areas and altered functional integration at different levels of perceptual hierarchies.

Dynamic causal modeling also allows for incorporating trial-wise computational quantities obtained from generative models applied to behavioral task data (e.g., precision-weighted prediction errors). This opens new avenues to derive a joint physiological–computational characterization of network dynamics during the performance of a task. Vossel et al. (137), for example, have demonstrated in healthy adults, using DCM for fMRI and the HGF, that during a combined attention/learning task (Posner's paradigm), the functional coupling between temporal and frontal regions was modulated by trial-wise estimates of attention (precision of the predictability of targets).

The fine temporal resolution of electrophysiological recordings provides much richer information on neurophysiological processes than fMRI. The generative model of DCMs for EEG exploits this information to describe how electrophysiological measurements are generated from cortical microcircuits (columns) with synaptic connections between different types of neurons (129). Validation studies in humans and animals have shown that DCM for EEG is capable of capturing short-term changes in synaptic efficacy, such as neuromodulation of glutamatergic receptor conductances, and distinguish different types of synaptic plasticity in cortical microcircuits (66, 132, 138–140) and, therefore, represents a promising approach to quantify the status of neuromodulatory systems in cortical microcircuits and may provide a foundation for clinically applicable tests.

Implications for Translational Studies

The pathomechanistic hypotheses of ASD that arise from the Bayesian brain perspective and the computational modeling techniques afford new avenues toward developing clinical tests for addressing problems of diagnosis and treatment in ASD. Initially, this will require a series of translational studies that evaluate the practical utility of different paradigms and models in patient studies.

In a first step, the preliminary evidence for disturbances in Bayesian inference in ASD (100–103) should be extended to multilevel hierarchical Bayesian learning paradigms in individuals with ASD. For this, the HGF framework provides a suitable platform as it allows for obtaining individual parameter estimates (encoding the influence of different forms of uncertainty or precision on learning) from relatively short behavioral measurements. At its simplest, one could adopt a cross-sectional design and test for group differences in these parameter estimates between ASD patients and adequately matched control groups. Additionally, the statistical comparison of different alternative models (within or beyond the HGF framework) could yield information about potential different subgroups of patients applying different cognitive strategies [cf. (113, 141)].

Model comparison also addresses an issue that has been a limitation in neuropsychological assessments of high-functioning individuals with ASD. Many tasks can be solved by applying different cognitive strategies, and this is not necessarily reflected by differences in average performance levels. Such hidden individual differences can be detected by formulating alternative computational models, each reflecting different cognitive strategies, and subjecting them to Bayesian model selection (62). Importantly, this can clarify whether any individual differences in task performance are due to the deployment of different cognitive strategies, or due to differences in implementing these strategies (141).

The diagnostic challenges in ASD particularly affect those individuals whose symptoms deviate from the classical clinical picture described by Kanner and Asperger, due to the factors described in the Section "Introduction." To test the hypothesis of a shared underlying pathomechanism despite diverse clinical presentations, the behavioral cross-sectional studies described above should be carried out both in children with the classical picture and diagnosed by the current gold standard (ADOS/ADI-R) and in individuals with less specific symptoms but diagnosed with ASD by experienced specialists.

The behavioral studies are ideally combined with the acquisition of functional neuroimaging data. This would enable the deployment of a model-based analysis, using computational

trial-wise quantities, such as precision-weighted prediction errors, to test for potential differences in neuromodulatory regions of interest [cf., Ref. (111)]. This investigation could clarify to what degree the impairment of different neuromodulatory systems across patients, causing disturbances in hierarchical inference, could represent a source of heterogeneity in individuals with ASD. Furthermore, one could also inform models of effective connectivity like DCM by trial-wise computational quantities [(137), cf., Ref. (142)], and test for group differences in Bayesian message passing in sensory hierarchies.

Notably, all of the above possibilities could be pursued in a multivariate setting, where individual parameter estimates are used to specify the feature space for subsequent supervised (classification or regression) or unsupervised (clustering) learning. This strategy is known as "generative embedding" (64, 65) and offers two major advantages over conventional machine learning applications that operate directly on features of the measured data. First, provided one has a good model, generative embedding typically results in substantially higher performance since the model is used as a theory-led feature selection device, which retains only dimensions of interest and discards irrelevant data features. Second, the classification or clustering results have a mechanistic interpretation since the dimensions of the feature space are given by specific model parameters. In ASD research, generative embedding based on hierarchical Bayesian models of behavioral data in conjunction with DCMs of effective connectivity might allow for designing powerful classifiers that support differential diagnosis. Additionally, an unsupervised approach would be of interest in order to identify potential mechanistically different subgroups. This is of special interest, since pharmacological therapy in ASD is presently trial and error; furthermore, many pharmacological substances targeting neuromodulatory mechanisms are available that have not yet found therapeutic use in ASD.

If initial studies indicate that discriminative parameters can be obtained and have high predictive power regarding diagnosis and/or treatment response, a necessary next step would be to turn the research-driven paradigms into easily applicable clinical tests. To minimize the influence of motivation and attention – potential limitations to this approach – and to ensure patient compliance and applicability in non-research settings, any cognitive paradigms would have to be relatively short or inherently appealing, with little or no need for specific instructions. Attractive candidate paradigms include tasks that neither require verbal instruction nor voluntary responses, such as implicit learning tasks or games that register involuntary responses such as eye movements (143) or electrophysiological mismatch negativity (144). The former could also be developed for infants (46). This would open up the possibility of characterizing potentially affected infants at a very early stage and following them up in longitudinal studies to study their developmental trajectories.

If modeling results imply that subgroups of patients exhibit pathophysiological mechanisms that can be targeted by existing interventions – for example, disturbances of specific neuromodulatory systems that could be targeted by selective drugs, or abnormal changes in the precision of beliefs about sensory inputs to which psychotherapeutic interventions might be directed – this would provide a foundation for planning randomized clinical trials. This could involve longitudinal clinical studies with pharmacological interventions, optimally in conjunction with tailored psychotherapeutic interventions (145) to guide the learning of new experiences in an optimally designed context in adults or combined with early behavioral training in children.

POTENTIAL BENEFITS FOR FUTURE CLINICAL PRACTICE

Clearly, solving the current clinical problems is an ambitious and long-term goal, which will take many years to reach. However, we believe that the framework outlined above has the potential of addressing the challenges described in the Section "Introduction."

Diagnosis

In the long run, clinically applicable, computerized trial-by-trial cognitive paradigms with accompanying generative models for the acquired data and "pushbutton" procedures for statistical inference could evolve into attractive computational assays providing estimates of ASD-specific disturbances in hierarchical Bayesian inference in individual patients.

Optimally, these assays should rest on paradigms, which are sufficiently appealing and independent of verbal instruction, such that they could be applied to young children. If successful, they could potentially replace the laborious gold standard ADOS/ADI-R diagnostics and provide an easier, faster diagnosis without reliance on trained specialists in expert institutions (*challenge i*). If such computerized assays are combined with response recording via eye tracking, they could become applicable in very young infants and potentially solve the problem of early recognition in high risk children at infant age (*challenge iii*). Similarly, they could be used for individuals without verbal skills at the severe end of the spectrum and help discriminate between ASD individuals with intellectual disability and those without spoken language but preserved intellectual and learning abilities (*challenge iv*).

Furthermore, such diagnostic assays could also solve the problem of recognizing autistic symptoms that are concealed by well-developed coping strategies in adolescence and adulthood (*challenge ii*). In this context, the Bayesian brain perspective has something to offer even before the development of novel diagnostic tests by suggesting a fundamentally novel theoretical explanation of the origin of autistic symptomatology. Its proposal of an abnormal balance in the precisions of sensory inputs and higher-order beliefs may facilitate a better understanding of the internal world of affected individuals, beyond the variety of observable manifestations. This novel explanatory model may support the education of clinicians with little previous exposure to individuals with ASD and help them grasp the potential range of clinical presentations. This alone may already help to reduce the number of unrecognized individuals with ASD (mainly in adult psychiatry).

One could speculate that, provided the research agenda outlined in this paper were successful, at some point in the future ASD might be redefined as "congenital perceptual inference disorder." This redefinition on the basis of a generic

pathomechanism might also affect other current diagnostic entities of adult psychiatry, such as schizoid or anankastic personality disorder. Given that their diagnostic criteria show major overlap with those of ASD, they could be regarded as foothills of the autism spectrum, with a possible relation to the same pathomechanism (146).

Behavioral and Psychotherapy

The hierarchical Bayesian perspective may be useful for a better understanding of existing therapies. For example, the effectiveness of early intensive behavioral training to foster social interaction and speech development (18, 19) can be understood as a result of gently enforcing the child's engagement in an interaction with the social environment, which is usually too noisy and dynamic for the affected child to be regarded as learnable and with which it, therefore, does not interact spontaneously. The core idea of the therapy is to reduce the complexity of social interactions to single, frequently repeated moments of interactions that slowly become interpretable (i.e., representable by a generative model) to the child and, therefore, manageable. From the Bayesian perspective, learning in ASD is more or less severely altered, but, nonetheless, possible throughout life, given optimal preconditions, such as little noise and dynamics in the exposed environment, and sufficient motivation for a high amount of repetitions. This view may trigger attempts to overcome the lack of behavioral therapies for severely affected adults (*challenge v*), as it suggests that these individuals should not be regarded as fundamentally limited in their capacity to learn. A continuation and adaptation of early behavioral training programs throughout life could slowly but steadily expand their scope of action and understanding. This approach is admittedly not without limitations. Actual intellectual disabilities – even if frequently overestimated – are certainly present, and a lack of motivation or resources are obvious obstacles, which cannot be overcome by theories alone.

Regarding autism-specific psychotherapy that goes beyond social skills training (*challenge vi*), two aspects can benefit from the explanatory appeal of the Bayesian brain perspective: psychoeducation, i.e., providing an explanation of the disorder, and psychotherapy in the strict sense, i.e., providing help in dealing and coping with the disorder. Concerning the former, and as observed ubiquitously across medicine, patients have a profound need to develop a concept of their disease and construct an explanation for their suffering. The perspective offered by the Bayesian brain theory can be useful in this regard, since it can be explained with reference to specific aspects of behavior and perception. It is the personal experience of the authors that this approach is useful for autistic patients and their relatives (but also their physicians) in order to establish a concept of their symptoms and suffering.

In treating autistic symptoms, two practical aspects take center stage: dealing with the perceived excessive complexity of everyday life and the fostering of developmental steps in the sense of expanding the scope of action. Generally, the principle "reduction of surprise by making the world predictable/understandable" may help patients deal with stress, sensory oversensitivity, and cognitive exhaustion by proactively seeking or creating predictable and controlled areas in both the personal and social domain. Complex social interactions can be rendered less perplexing or surprising by helping the patient to develop a generative model, by providing explicit explanations for the behavior of others and teaching them about possible reactions to chosen actions. In order to expand the scope of possible actions, the lack of spontaneous exploration and intuitive learning by generalization can be compensated by precise step-by-step instructions toward new actions that can be strengthened by excessive repetition. The generalization of such new abilities could be facilitated by explicit elaboration and memorization of the underlying abstract principle behind the behavior.

In the future, model-based estimates of individual abnormalities in hierarchical Bayesian inference could help facilitate the development of novel targeted psychotherapeutic interventions and subject-specific strategies for coping with cognitive deficits. For example, for patients where the relative overweighting of low-level vs. high-level precision (cf. Eq. 1) primarily derives from a deficit at high levels – for example, flat priors due to an overestimation of volatility – suitable interventions and coping strategies are likely to differ substantially from patients in whom overestimation of low-level sensory precision is the dominant problem. In the former case, inadequate higher cognitive levels of abstraction (flat top-down priors) might be sharpened by explicit teaching of abstract principles behind complex everyday processes, to buildup higher model levels without having to rely on the intuitive extraction of principles from exposure and imitation. In the latter case, efforts to reduce sensory overload by adaptions to the surrounding environment (at home, school, or work) seem more paramount.

The development of autism-specific psychotherapy of comorbidities (*challenge vii*) can likely profit from the novel explanatory perspective of ASD. Especially comorbidities, such as low mood or anxiety, can be understood as consequences rather than as incidental comorbidities with pathomechanisms that are completely independent from those of ASD. Their psychotherapy could also become more specific if patients understand these symptoms as a consequence of a fundamental perceptual problem, which causes chronic cognitive stress.

Pharmacotherapy

Pharmacotherapy, in ASD, is presently mostly off-label (*challenge viii*) and, in the absence of predictive tests, necessarily relies on trial and error (*challenge ix*). The use of the approved dopamine receptor antagonist (risperidone) is of questionable benefit for cognition in ASD, as its antagonistic effects at dopamine receptors may interfere with precision-weighting of prediction errors, and thus updating of priors, in high-level regions of the cognitive hierarchy such as prefrontal cortex (91), which are critical for the development of abstract representations. Indeed, empirical studies demonstrate that core symptoms of ASD do not benefit from this medication (147). Perhaps not surprisingly, this purely symptomatic approach is rarely subjectively experienced as helpful by patients. Off-label use of pharmacotherapy mainly consists of stimulating different neuromodulatory systems that may be involved in precision-weighting of prediction errors: there is evidence of benefit by dopaminergic and noradrenergic stimulation with methylphenidate (25) and of purely noradrenergic stimulation with atomoxetine (148). The

evidence for benefit of treatment with selective serotonin reuptake inhibitors is mixed (149). Several recent studies document first promising results for cholinergic stimulation (150) and oxytocin application (151). Future clinical studies in patient subpopulations, which are stratified by model-based indices of pathophysiology, might enable to select more effectively among available treatments; this could benefit in particular from computational functional neuroimaging analyses with potential sensitivity for alterations of neuromodulatory systems (118).

CONCLUSION

Recently developed theories of ASD, which posit a fundamental perceptual abnormality due to an aberrant balance of precision estimates in hierarchical Bayesian learning, offer a novel and rich perspective on this spectrum disorder. In this paper, we have described the implications of this perspective for addressing central problems in the contemporary clinical management of ASD. We suggest that generative models of behavioral and functional neuroimaging data could play a key role in establishing novel objective diagnostic tests, which disambiguate patients characterized by different causes of the proposed perceptual aberration. Such models could become useful for selecting between existing pharmacological interventions and for developing novel behavioral/cognitive training programs. Close collaborations between clinicians and computational scientists will be essential for conducting the necessary translational studies.

AUTHOR CONTRIBUTIONS

HH, MS, and KS contributed to the conception, the drafting, and the revision of the manuscript. HH designed the figures.

FUNDING

This work was funded by the University of Zurich (HH, KS), the René and Susanne Braginsky Foundation (KS), and the "Netzwerk Schizophrenie" Foundation (MS).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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