Title

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Journal

World Psychiatry, 23(1)

ISSN

1723-8617

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Publication Date

2024-02-01

DOI

10.1002/wps.21159

Peer reviewed

Functional magnetic resonance imaging in schizophrenia: current evidence, methodological advances, limitations and future directions

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Functional neuroimaging emerged with great promise and has provided fundamental insights into the neurobiology of schizophrenia. However, it has faced challenges and criticisms, most notably a lack of clinical translation. This paper provides a comprehensive review and critical summary of the literature on functional neuroimaging, in particular functional magnetic resonance imaging (fMRI), in schizophrenia. We begin by reviewing research on fMRI biomarkers in schizophrenia and the clinical high risk phase through a historical lens, moving from case-control regional brain activation to global connectivity and advanced analytical approaches, and more recent machine learning algorithms to identify predictive neuroimaging features. Findings from fMRI studies of negative symptoms as well as of neurocognitive and social cognitive deficits are then reviewed. Functional neural markers of these symptoms and deficits may represent promising treatment targets in schizophrenia. Next, we summarize fMRI research related to antipsychotic medication, psychotherapy and psychosocial interventions, and neurostimulation, including treatment response and resistance, therapeutic mechanisms, and treatment targeting. We also review the utility of fMRI and data-driven approaches to dissect the heterogeneity of schizophrenia, moving beyond case-control comparisons, as well as methodological considerations and advances, including consortia and precision fMRI. Lastly, limitations and future directions of research in the field are discussed. Our comprehensive review suggests that, in order for fMRI to be clinically useful in the care of patients with schizophrenia, research should address potentially actionable clinical decisions that are routine in schizophrenia treatment, such as which antipsychotic should be prescribed or whether a given patient is likely to have persistent functional impairment. The potential clinical utility of fMRI is influenced by and must be weighed against cost and accessibility factors. Future evaluations of the utility of fMRI in prognostic and treatment response studies may consider including a health economics analysis.

Key words: Schizophrenia, functional magnetic resonance imaging, biomarkers, negative symptoms, functional outcomes, cognition, treatment response, therapeutic mechanisms, precision medicine, clinical utility

(World Psychiatry 2024;23:26–51)

While functional neuroimaging in schizophrenia emerged in the literature somewhat later than structural neuroimaging, its promise was just as great or greater, as have been its challenges. Fortunately for the field, and for people suffering from schizophrenia, the maturational arc of this technique is in its ascendancy, with a number of new developments that have accelerated our understanding of brain function in this illness from the group to the subgroup to the individual level.

The present paper aims to serve as a comprehensive review of functional neuroimaging in the various phases of schizophrenia. The focus is on functional magnetic resonance imaging (fMRI), both resting state and task-based, rather than other types of functional neuroimaging – e.g., positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG), and arterial spin labeling (ASL). We provide a critical summary of the literature on fMRI in schizophrenia, including diagnostic markers, neural correlates of negative symptoms and cognitive deficits, and markers of treatment resistance and therapeutic response. The utility of fMRI to understand therapeutic mechanisms, guide precision treatment, and dissect patient heterogeneity is also reviewed. Lastly, methodological considerations and advances, limitations, and future directions of research in the field are discussed.

Neuroimaging research in schizophrenia began with the advent of computed tomography (CT) and then MRI scans, which demonstrated that there were structural differences in the brains of people with that diagnosis, considered as a group, compared to healthy controls[1]. These early investigations were followed by functional neuroimaging studies using PET and then fMRI, revealing that brains of people with schizophrenia, again considered as a group, also functioned differently[2-5]. Over time, the field has shifted its focus from regional brain activation to more global activation and connectivity. Despite a wealth of evidence for differences in brain activation and connectivity between samples of people with schizophrenia and samples of healthy controls, findings are variable[6]. fMRI-based diagnostic markers remain elusive, but recent work using machine learning approaches for diagnostic prediction, or aimed at the identification of dimensional, transdiagnostic brain-based biomarkers, holds promise[7,8].

Regarding the various phases of schizophrenia – clinical high

risk (CHR), first episode and chronic – there has been an increasing focus on the first episode and CHR phases. The field began studying chronic patients in the late 1980s and 1990s, and then added the study of first-episode patients some years afterward, followed by the study of CHR individuals several years after that [9,10]. Similar brain networks seem to be implicated across these populations; however, there is often greater confidence with fewer confounds in earlier illness phase subjects, while sample sizes and statistical power are typically larger in later phase patient studies. In recent years, collaborative multi-center research has been critical to advance our understanding of these different illness phases [11]. Larger sample sizes, achieved via "pooling" of data – e.g., via the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium[12,13] – have helped increase statistical power, and clarified the robustness of findings previously achieved using smaller samples.

Given their strong associations with functional outcomes, the neural correlates of negative symptoms and cognitive deficits have been significant areas of investigation in schizophrenia[14,15]. Potential neural markers of negative symptoms have been identified in fMRI studies of early and chronic schizophrenia, but results suggest that they may vary by symptom construct, and that inconsistencies in the conceptual framework underlying the assessment of negative symptoms may hamper progress[15,16]. Regarding cognitive impairments, task-based fMRI has been instrumental in allowing for real-time assessments of brain function while patients complete cognitive tasks in the scanner. Early work characterizing small patient groups produced robust patterns of either heightened or reduced neural activation; however, recent work shows that there may be heterogeneity among patients in terms of which circuits or networks are engaged during tasks[17,18], just as there is such variability among individuals without psychiatric illness[19,20]. Different people may use different neural strategies to complete the same cognitive tasks[21-23]. Further, neural activation patterns during cognitive processing may relate to cognitive performance rather than diagnosis[24].

The heterogeneity of schizophrenia is a critical clinical consideration, which is highlighted throughout this review, acknowledging that no two patients are exactly alike. For much of the history of neuroimaging investigation, schizophrenia has been treated as a single construct using categorical, group-based approaches, despite significant variability among positive and negative symptom expression, neurocognitive and social cognitive performance, treatment response, functioning, and many other facets of the illness[25,26]. There is a recognized need for dimensional approaches across cases and controls, and for the transdiagnostic identification of brain-behavior relationships[27,28]. Of late, the application of multivariate and multimodal data-driven integration approaches and machine learning models in large, consortia-based samples, to identify brain-based biomarkers of diagnosis, symptom constructs, functional outcomes, treatment response and beyond, has shown how clinical heterogeneity can be linked to biological heterogeneity, and provided some hope for potential clinical utility of fMRI[8].

Potentially greater success in relating neural activation to behavioral constructs may be forthcoming through the identification of subtypes or biotypes of illness that may have different outcome trajectories and prognoses[29]. If these are established at the first episode, they may guide decisions around treatment, particularly those interventions which are expensive and resource intensive[30]. fMRI markers may be particularly informative regarding treatment resistance and response, understanding therapeutic mechanisms, and guiding precision treatment.

Perhaps the greatest chance of successful clinical application of fMRI is in guiding pharmacological and neurostimulation treatment. With respect to treatment response, replicated resting state findings identifying the neural circuitry correlates of non-response to conventional antipsychotics could accelerate the use of clozapine[31], a life-saving medication for some, rather than subjecting patients to multiple unnecessary antipsychotic trials. In addition, an understanding of therapeutic mechanisms using pre/post designs in clinical trials can better inform clinicians of potential benefits and harms of particular treatments, and provide the opportunity for improvement in therapeutic development. Finally, an understanding of individual differences can be useful for therapeutic targeting, e.g., using neurostimulation approaches in a personalized manner based on an individual's functional connectivity profile[32,33].

Methodological considerations and advances are also discussed in this paper, covering developments in experimental design, data acquisition, and pre-processing and analytical choices. Notably, significant developments in scanner hardware have allowed for higher resolution acquisitions in shorter periods of time, improved motion correction, and harmonization across sites to support multicenter consortia-based research, an essential advance that has led to more replicable findings for the field[34,35]. In conjunction, precision medicine-based approaches that are now being applied to fMRI, such as deep phenotyping via longer resting state fMRI scans, may more definitively characterize individual variation in brain activity and reliable functional connectivity features, to support individualized biomarker identification and targeting of neurostimulation treatments[36,37].

Availability and advances in reproducible neuroimaging software pipelines, facilitated by code sharing and open science initiatives, have also allowed for more standardized fMRI analyses across labs[38,39]. Data pre-processing and analytical decisions substantially affect neuroimaging results and conclusions[40], emphasizing the importance of such developments for reproducibility of findings. Advances in network theory and the use of multivariate analyses have also allowed for interpretation of the brain's function as a set of networks, and provided insight into collinearity across brain regions and behavioral tasks, mitigating the multiple comparison problem[41-43]. Additionally, tools for moving analyses from volume- to surface-based approaches have better aligned with our knowledge of brain anatomy and allowed for the assessment of individualized brain topography and connectivity profiles[44,45].

While fMRI is providing valuable insights into the pathophysiology of schizophrenia, the limitations of the field are many. Technical limitations and physiological constraints of fMRI, sources of noise and artefacts, the multiplicity of analytical choices, small

sample sizes, the heterogeneity of the illness, and sampling bias related to illness severity or comorbidities have all contributed to reproducibility and generalizability issues[46]. The relationship between cost of fMRI and clinical utility, and the accessibility of the technology for those who live in more remote areas, are important factors as well. The field is also facing challenges regarding the conceptual framework underlying much of the fMRI research to date, for example with a shift from categorical to dimensional and individualized approaches[47,48].

Despite these limitations, the field is far ahead of where it was even a decade ago. Recent publications have brought fMRI reproducibility and generalizability issues to the forefront once more[49]. However, major advances in methodology and standardization, including via the Human Connectome Project, multi-center collaborations which dramatically increase sample sizes to better deal with type 1 and 2 error, reproducible methodologies, and progress in data-driven and precision-based approaches, have given rise to a new age of fMRI research in schizophrenia[13,34,38,50]. The increasing use of fMRI in clinical trials has also been an important development, with many potential future directions in terms of guiding treatment approaches. Relatively new understanding of the value of within-person sampling to generate more robust findings at the individual level may also change our thinking about how we use this technology[51].

This paper comprehensively reviews findings in each of these areas relevant to fMRI in schizophrenia, critically considering both important advances and limitations. Overall, it serves to summarize where the field of fMRI in schizophrenia has been, where it is at present, and its future potential.

DIAGNOSTIC MARKERS

Case vs. control regional and whole brain activation

The application of fMRI for examining brain-based abnormalities in schizophrenia was preceded by approximately two decades of work with functional neuroimaging methods such as xenon inhalation and PET. These latter studies laid the foundation for methods and scientific themes that were carried forward to fMRI investigations. Similarly, ideas from cognitive neuroscience, which intertwined with xenon inhalation/PET and EEG, heralded the advent of fMRI. Contextualizing the emergence of fMRI studies of schizophrenia in the mid-1990s requires discussion of findings from and methodologic challenges inherent to those other neuroimaging modalities.

In one of the first functional imaging studies of schizophrenia, Ingvar and Franzén used ^{133}xenon inhalation to document decreased blood flow to frontal brain regions[52]. In the late 1970s and early 1980s, this idea was carried forward with cerebral blood flow and glucose metabolism studies at rest, but especially using cognitive paradigms such as the Wisconsin Card Sorting Test to examine changes in cerebral blood flow during a cognitive challenge[2,3,53]. These early studies led to the conceptualization of schizophrenia as an illness characterized by regionally specific frontal hypoactivation, primarily in the dorsolateral prefrontal cortex (DLPFC) during task engagement, but also in the anterior cingulate cortex during attentional control[54].

While these studies aimed to establish pathophysiologic markers of schizophrenia, others subtyped the illness based on findings including activation of Broca's area and subcortical structures during hallucinations, and greater involvement of temporal lobe activation in the context of the presence of disorganization and formal thought disorder[55-58]. Though not designed for establishing diagnostic markers, these early studies provided a scientific framework for demarcating schizophrenia with neuroimaging measures.

The advancement of image processing methods, and analytic approaches such as statistical parametric mapping, allowed standardized hypothesis testing of regionally specific neural dysfunction[59]. These advances further helped fMRI to carry forward the work of xenon inhalation/PET studies, but without the radiation exposure. Early fMRI studies characterized diagnostic differences in patients with schizophrenia relative to healthy controls across a variety of cognitive states. This included further support for deficits in DLPFC functioning during working memory, with specificity for schizophrenia, building upon earlier observations of "hypofrontal" blood flow[4,5]. Related fMRI studies of executive functioning reported decreased anterior cingulate cortex activation during attentional monitoring[60]. Additional findings across other cognitive domains and clinical contexts included decreased superior temporal gyrus activation during auditory processing[61], increased temporal lobe activation during hallucinations[62], abnormal limbic activation during facial emotion processing[63], and abnormal sensorimotor activation during pursuit eye movements[64].

Findings from case-control fMRI studies of schizophrenia advanced our understanding of network-related abnormalities that characterize the syndrome. Beyond regionally specific dysfunction of structures, such as the DLPFC during executive processing, meta-analyses illustrated large-scale dysfunctional activation across a network of regions including subcortical structures, cognitive control regions, and the frontoparietal network[65,66]. Similarly, fMRI and PET studies of episodic memory demonstrated abnormal DLPFC-hippocampal activation during recall, implicating impaired frontal-hippocampal coactivation that extends beyond a regionally specific deficit[67,68].

Meanwhile, concurrent evidence began to isolate synchronous functional networks that characterize the intrinsic functional architecture of the brain, independent of task-based activation, starting with the identification of the default mode network (DMN)[69-71]. Functional connectivity studies of schizophrenia demonstrated abnormal coupling between the DLPFC and the hippocampus in relation to psychosis and working memory[72-74], and abnormal intrinsic thalamocortical connectivity at rest[75,76]. Novel data-driven methods for fMRI analysis, reviewed in more detail below, also allowed for the identification of large-scale network-specific abnormalities in schizophrenia, including the DMN[77]. These findings supported the decades-old "dysconnectivity" hypothesis of schizophrenia[78]. While not directly quantifying diagnostic specificity,

this first wave of neuroimaging via PET and fMRI established key pathophysiologic markers of schizophrenia that have been further leveraged by more advanced analytic methods.

Case vs. control modular and global connectivity

The demonstration of distributed co-activation across the brain, and the identification of a set of replicable resting state brain networks, drove a shift from studies examining local activation of particular brain regions in schizophrenia vs. healthy controls to functional connectivity studies exploring how different brain areas interact and form networks. With this shift came the rise in popularity of resting state fMRI, which is ideally suited for examining intrinsic connectivity.

Early studies of functional connectivity utilized undirected seed-based approaches, correlating the activity over time between selected regions of interest. Many focused on the DMN, as regions comprising this network were found to be implicated in self-referential thinking and mentalizing. Both hypoconnectivity[79,80] and hyperconnectivity[81,82] within the DMN in people with schizophrenia vs. healthy controls were reported[83]. These studies were followed by seed-based whole-brain voxel-wise approaches to examine connectivity more globally.

Seed-based analyses of resting state connectivity demonstrated widespread connectivity abnormalities in schizophrenia compared to healthy controls, but results were mixed regarding locality of seed regions and directionality (i.e., hypo- or hyper-connectivity)[6]. Earlier evidence suggested that schizophrenia is related to hypoconnectivity, particularly of the frontal lobe, in comparison to healthy controls[84]. Aligning with this, a meta-analysis of whole-brain seed-based resting state connectivity demonstrated hypoconnectivity within and between multiple networks, including the DMN, ventral attention/salience network, and thalamus networks in schizophrenia compared to healthy controls[85]. These findings support a large-scale disconnected brain networks model of schizophrenia.

Effective connectivity differs from typical functional connectivity, as it is based on a mechanistic model of causal influence between regions of the brain[86]. Dynamic causal modeling[87] is a technique which has been used to demonstrate differences in effective connectivity of the DMN in first-episode psychosis[88], of the frontoparietal network during working memory performance[89], as well as of prefrontal regions in relation to cognition and clinical symptoms[90] and of the hippocampus in relation to clinical symptoms[91] in schizophrenia vs. healthy controls.

Recent work using spectral dynamic causal modeling of resting state fMRI fronto-striato-thalamic circuits suggests that dysconnectivity of the subcortex is present in first-episode psychosis, and dysconnectivity between the cortex and subcortex is seen in later stages of schizophrenia[92]. Local connectivity between spatially adjacent regions has also been examined in schizophrenia using regional homogeneity, with meta-analyses showing abnormal localized connectivity[93,94], including in the medial prefrontal cortex within the DMN[95].

More complex, multivariate approaches, such as spatial independent component analysis (ICA), allow for data-driven exploration of regions with temporal synchronicity across the whole brain to parcellate systems or networks, without pre-selection of regions of interest[96,97]. ICA has been used to detect altered functional connectivity in people with schizophrenia compared to healthy controls, including in the DMN[77,98], frontoparietal/cognitive control network[99,100], and salience network[101]. A meta-analysis of (whole-brain or network-specific) seed-based functional connectivity studies based on ICA brain templates in schizophrenia vs. healthy controls revealed hypoconnectivity between regions from multiple networks, including the DMN as well as auditory and somatomotor networks[102].

Graph theoretical approaches provide a way to quantify the organization and function of brain networks modeled as a set of nodes and edges, including global and local properties[103,104]. Evidence from graph theoretical analyses of functional connectivity suggests that the brains of people with schizophrenia show aberrant network properties, including reduced efficiency, disrupted hub connectivity, and altered modularity compared to healthy controls[105], generally exhibiting a disruption in the balance of regional integration and segregation (i.e., reduced small-worldness)[106-108]. A meta-analysis of functional graph-analytical studies in schizophrenia demonstrated decreased small-worldness, as well as reduced local organization/efficiency, compared to healthy controls[109].

More recently, dynamic connectivity approaches have been used to explore time-varying connectivity states or modes in schizophrenia, with the suggestion that the variability of functional connectivity findings in this disorder may be driven in part by the use of static analyses[110]. Dynamic functional connectivity analyses have provided evidence for people with schizophrenia spending more time in weaker between-network connectivity states[110] and less in switching between states[111,112]. They have also further supported DMN dysfunction[113,114].

Converging evidence implicates dysconnectivity of the DMN, frontoparietal and salience networks, including the striatum, as well as of cortical-subcortical interactions (e.g., thalamocortical) as potential diagnostic markers of schizophrenia. Indeed, a transdiagnostic multimodal meta-analysis identified schizophrenia-specific dysconnectivity of the DMN, frontoparietal, salience and limbic networks, with converging functional dysconnectivity and reduced gray matter volume in the insula, striatum and thalamus[115].

Though an abundance of fMRI-based case-control differences have been observed, the search for clinically diagnostic functional imaging markers of schizophrenia continues. Inconsistent findings may be a consequence of the heterogeneity present within schizophrenia and across people with schizophrenia and healthy controls, which may be better characterized using dimensional or more individualized approaches rather than categorical ones[8]. Machine learning approaches hold promise for parsing heterogeneity and identifying predictive neuroimaging features.

fMRI biomarkers of schizophrenia

With all the evidence of functional connectivity differences in schizophrenia, and with the growth of machine learning approaches, the question of whether a brain scan could be used to diagnose schizophrenia reliably has been a concern since the early days of this century. One of the earliest studies[116] used a sample of task-based fMRI data from an auditory oddball task in approximately 20 individuals with schizophrenia, bipolar disorder, or no psychiatric disorder. Using temporal lobe and default mode networks and some basic clustering approaches, the authors reported that they were able to classify the participants with 90% or higher accuracy. Although data-driven techniques are reviewed later in relation to heterogeneity, we focus here on machine learning through the lens of diagnostic classification.

Part of the attraction of machine learning approaches is the possibility of scanning an individual who is either at risk or whose diagnosis is in dispute, and automatically getting a high-confidence, objective judgement as to a patient's diagnosis[8,117]. There have been a multitude of studies over the past few decades attempting to develop such an algorithm. A review of studies using the support vector machine (SVM) algorithm to classify functional or structural scans found that most of them reported an accuracy of 80% or higher in distinguishing schizophrenia cases from controls[118]. While SVM was the dominant algorithm in the past, deep learning techniques have shown equivalent or improved promise in being able to distinguish schizophrenia cases from healthy controls on the basis of a scan from a neuroimaging dataset[119,120].

With such promising data over almost 20 years, why do we not have diagnostic scans for schizophrenia in use already? There are a number of problems. Notably, many of the studies, including some recent ones, have focused on a very small number of subjects, 20 or 30 per diagnostic group. Smaller samples are prone to overfitting in their models, and their results often do not generalize to a larger dataset[121]. Moreover, a model built on a dataset from one particular type of scanner and scanning protocol often does not perform well on data collected in another setting[122]. As larger and more heterogeneous resting state datasets are becoming increasingly available, machine learning algorithms which can generalize across the varieties of scanning settings around the world are being developed[123].

A further limitation is that confirming whether someone has schizophrenia or no mental disorder is rarely of clinical utility. Studies to date have generally worked with clinically diagnosed and medicated individuals with schizophrenia and contrasted them to age- and gender-matched individuals with no history of psychiatric disorders. This facilitates the machine learning training process, as whether the algorithm provides the correct answer is determined by the clinical diagnosis. However, this does not match the clinical situation. Predicting whether someone who is currently not on antipsychotic medication is likely to develop a full psychotic disorder, or which of several possible diagnoses may apply, is where the classification systems could be more useful. This has been addressed by studies showing that schizophrenia and bipolar disorder, and to some extent schizoaffective disorder, are separable[124,125], or that a system trained to use fronto-striatal features in schizophrenia will not falsely identify obsessive-compulsive disorder or any other psychiatric diagnosis[126]. Studies that recruit medication-naïve or first-episode participants are also showing promise[127], and getting sufficient samples of people at risk, to predict who does or does not develop psychosis, is a current international interest[128].

Just as the machine learning algorithms have to be trained to identify schizophrenia while not being confused by the heterogeneity of scanner characteristics, they also need to be trained across a wide set of diagnoses and clinical scenarios, in order to help the clinical process. A biomarker of chronic schizophrenia may not predict conversion to psychosis in CHR cases, or response to a given treatment, or which circuits are the most amenable to neuromodulation. But the capacity of machine learning approaches to address these questions is developing, as predicting prognostic trajectories for high-risk or first-episode subjects is an active area of exploration[129–131].

fMRI biomarkers in the clinical high risk phase

Early studies exploring resting state functional connectivity in CHR populations identified DMN hyperconnectivity[132] or a failure to suppress the DMN under high memory load[133] relative to healthy comparison participants. Later, a greater DMN connectivity was linked to poor insight[134].

Dysconnectivity within the cortico-striatal-thalamo-cortical networks has been reported by multiple groups[132,135-143] – specifically, hypoconnectivity in corticostriatal, thalamocortical and thalamo-cerebellar areas, and hyperconnectivity within sensorimotor cortical areas. Corticostriatal[137] and cerebellar-talamo-cortical[143] dysconnectivity has been linked to positive symptoms in CHR.

CHR participants in the North American Prodrome Longitudinal Study second cohort (NAPLS-2)[144] who later converted to psychosis had more prominent hypoconnectivity between the thalamus and prefrontal and cerebellar areas, and more pronounced thalamic hyperconnectivity with sensorimotor areas[135]. Disrupted functional connectivity of the insula with other hubs in the salience network[145] has also been associated with psychotic conversion. Further, adding measures of within- and between-network connectivity to validated clinical predictors from the NAPLS psychosis-risk calculator[146] was found to improve model performance[147].

More recently, a study from the Shanghai At Risk for Psychosis (SHARP) program[128], including a large unmedicated CHR sample, found that abnormal modular functional connectome organization predicted psychotic conversion, replicating prior work in a smaller medicated sample[148]. Using longitudinal data from NAPLS-2, it was found that CHR participants who later converted to psychosis showed a reduction in global efficiency and an increase in network diversity relative to CHR participants who did not convert, and this finding was primarily driven by the DMN[149].

Resting state fMRI data from NAPLS-2 were also used in a high-

dimensional brain-wide functional mediation framework to identify brain regions mediating the relationship between baseline behavioral symptoms and conversion to psychosis among CHR subjects[150]. Positive mediators were primarily distributed in the sensorimotor system, insular and opercular areas, and the striatum. Negative mediators were mainly located in the DMN and visual system[150].

Clearly, emerging functional connectivity research in the period before the onset of psychosis is revealing evidence of dysconnectivity in brain networks known to be relevant in information processing, neurocognition and psychosis. Replication of these findings in additional samples – including NAPLS-3 and the Psychosis-Risk Outcomes Network (ProNET) – will be important, along with the implementation of creative analytic techniques, to better understand the evolution, early identification and potentially pre-emptive treatments in the early stages of emerging psychotic illness.

fMRI markers of negative symptoms

Negative symptoms are a major determinant of poor functional outcome in people with schizophrenia[151-156]. Both first- and second-generation antipsychotics have limited benefit for this illness dimension[157-159]. The elucidation of the neural networks that serve as the substrate for these symptoms may be important for the development of new treatments.

A critical issue in the investigation of the neural basis of negative symptoms is the conceptual framework underlying their assessment. Of particular importance is the separation of negative symptoms into primary and enduring (deficit symptoms) vs. secondary ones. Deficit symptoms are regarded as intrinsic to the illness, whereas secondary negative symptoms may be due to exacerbations of psychosis, extrapyramidal side effects of antipsychotics, depression and/or understimulating environments[160-162]. There are limited functional imaging studies focused on the deficit syndrome. However, one study reported aberrant cerebellar neural activity and cerebro-cerebellar functional connectivity, involving executive dysfunction, in patients with this syndrome[163].

A major obstacle to the focus on the deficit syndrome in neuroimaging studies is the need to use trained investigators to administer an extensive diagnostic interview[164]. This has led to the development of the concept of persistent negative symptoms[157]. This concept also tries to minimize the heterogeneity associated with broadly defined negative symptoms, through the restriction to those that persist for six months or more and are present during periods of clinical stability and in the absence of prominent positive, depressive or extrapyramidal symptoms[157]. Here too there is a paucity of functional neuroimaging studies. The extant literature largely focuses on negative symptoms without invoking the deficit syndrome or persistent negative symptoms conceptual frameworks.

According to a common conceptualization, there are three subgroups of people with schizophrenia along a continuum from positive to negative symptoms: predominantly positive, predominantly negative, and mixed[161]. Indeed, functional connectivity between the salience and default mode networks has been related to both positive and negative symptoms[165]. Alternatively, negative symptoms may be conceptualized as a disease dimension, suggesting that there are distinct brain networks involved in negative vs. positive symptoms. In this latter context, and for patients with chronic schizophrenia, altered DLPFC-cerebellum[166], striatal-orbital medial frontal cortex[167], and medial fronto-temporal[168] functional connectivity have all been associated with negative symptoms. In patients earlier in their disease course, altered functional connectivity between crus II of the cerebellum and the anterior supramarginal gyrus has been associated with negative symptoms[169]. Early in the disease course, but not at a more chronic stage, greater negative symptom burden has also been associated with decreased activation in the cerebellum during a verbal Stroop task[170]. Irrespective of the stage of illness course, an inverse correlation has been observed between negative symptom burden and activation of motor cortex, including the supplementary motor area and precentral gyrus[170].

The various negative symptoms may also differ in their neural correlates. Indeed, in a fMRI study using a two-tone auditory oddball task, the severity of alogia, avolition/apathy and anhedonia/asociality was inversely correlated with blood oxygenation level-dependent (BOLD) signal during the target tone in distinct sets of brain regions[16]. There was an inverse correlation between anhedonia/asociality and the activity of the posterior cingulate and precuneus, which are typically considered to be part of the DMN. The severity of alogia was instead associated with decreased activity in the bilateral thalamus, right caudate and left pallidum, suggesting that this symptom may reflect a deficit in the ability to engage in voluntary motor behavior[16].

fMRI markers of cognitive deficits

Cognitive deficits are a core feature of schizophrenia and represent one of the main obstacles to clinical and functional recovery in affected individuals. Deficits are present both in general intelligence and in specific neurocognitive domains, as well as in social cognition[14]. Both social and non-social cognitive impairments appear to be distinct constructs from those of symptom profiles[171,172], and have been proposed as potential treatment targets[173,174].

Overall cognitive performance in schizophrenia is reported to be on average two standard deviations below that seen in unaffected individuals[175]. Impairments are also typically seen in specific domains, including memory, verbal and visual learning, executive functions, attention, and processing speed[176,177]. Particularly impairment in working memory, which involves the short-term storage and manipulation of information, has been proposed as a core deficit in schizophrenia[178]. Processing speed, which refers to the amount of time it takes for an individual to process and accurately respond to information in his/her environment, has also been reported as one of the most affected neuropsychological functions in schizophrenia[179]. Due to the ease of

use of processing speed assessments, they have been proposed as potentially useful tools for screening in clinical settings, or for the evaluation of specific interventions[179]. There is significant evidence that cognitive deficits are already present at the time of the first episode of psychosis[180], as well as in CHR individuals, albeit with high variability within different cognitive domains[181-183]. Whether further cognitive decline occurs after the first psychotic episode is less clear, and studies have reported both decline and amelioration[184,185].

Social cognition represents the cognitive capability to process, store and apply information about other people and social situations. Individuals with schizophrenia have difficulties in identifying emotions, feeling connected and reacting emotionally to others, and inferring people's thoughts[186-189]. As such, impairments in social cognition have been demonstrated to be a key correlate and predictor of functional outcome[173,174]. Social cognition is often divided into lower-level (e.g., emotion recognition and simple mental representation) and higher-level mentalizing (e.g., belief and intention inference; theory of mind) processes[173,190-192].

Evidence suggests that social cognition and neurocognition are distinct but related constructs[173,193], with meta-analytic results showing a stronger relationship between social cognition and functional outcomes[174,194]. Meta-analyses in CHR individuals have also demonstrated deficits across social cognitive domains, including emotion processing and theory of mind[195,196].

Neurocognitive impairments were established early on as fundamental features of schizophrenia, resulting in a wealth of neuroimaging studies examining cognition[1]. Initial fMRI studies focused on regional activity during specific cognitive tasks, demonstrating aberrant activation in the DLPFC during working memory tasks in people with schizophrenia vs. healthy controls[197,198]. Variability in such findings was also soon evident, including both decreases and increases in DLPFC activation during working memory performance, prompting meta-analyses to integrate results and identify potential moderating factors[199].

Meta-analyses of fMRI studies have focused on particular domains of neurocognition, including working memory, episodic memory, and executive functioning. A meta-analysis on DLPFC activation during working memory tasks[199], and a selective review of fMRI studies of working memory deficits in schizophrenia[200], support the role of DLPFC dysfunction in working memory impairments in schizophrenia. An early meta-analysis of fMRI studies of working memory in schizophrenia also identified abnormal activation of the DLPFC, anterior cingulate cortex, and insula compared to healthy controls[66]. More recently, a meta-analysis corroborated dysfunction of these areas, as well as of the posterior parietal cortex and supplementary motor area, noting that these identified regions are nodes of the cognitive control network and salience network[201].

Meta-analyses have also focused on fMRI studies of episodic memory in schizophrenia, identifying aberrant activation in regions including the left inferior prefrontal cortex, hippocampus, and left cerebellum versus healthy controls[202]. A meta-analysis of 41 functional neuroimaging studies of executive functioning (sometimes referred to as cognitive control) in schizophrenia revealed decreased activation in the DLPFC, anterior cingulate, and thalamus[65].

These findings have been largely confirmed in a review of neural correlates across neurocognitive domains in different phases of schizophrenia, noting that many of the neural abnormalities evident in chronic schizophrenia appear to be present to some degree prior to illness onset[203]. In relation to this, a meta-analysis of fMRI studies using neurocognitive tasks in CHR individuals demonstrated reduced activation of the inferior parietal lobule and medial frontal gyrus compared to healthy controls, and only of the inferior parietal lobule when looking at a subset of four studies using working memory tasks[204]. The regions of the brain implicated in these different cognitive functions are widely distributed and often overlapping[203]. Indeed, these deficits may not be discrete[205], and the DLPFC has been suggested as a potential common substrate for many cognitive impairments[206].

As mentioned, neuroimaging studies in schizophrenia suggest that cognitive performance depends on distributed brain systems or networks, rather than isolated regions[207]. A systematic review examining associations between resting state functional connectivity and neurocognition within and across domains found that aberrant connectivity between regions of the cortex and subcortex (cortico-cerebellar-striatal-thalamic loop) was associated with deficits in executive functioning, working memory, and processing speed, and that abnormal connectivity between regions of the DMN and the frontoparietal (e.g., DLPFC) and cingulo-opercular (e.g., anterior cingulate cortex) networks was related to multiple cognitive domains[208]. Notably, unique associations between particular cognitive domains and specific abnormalities in functional connectivity were not detected, supporting the idea of a disruption in shared mechanisms across neurocognitive domains resulting in generalized cognitive impairments observed in people with schizophrenia[208].

A recent meta-analysis also reviewed studies looking at the association between structural brain metrics and cognitive domains in schizophrenia, and mapped these structural findings onto resting state functional brain networks[209]. The frontoparietal (cognitive control) network was associated with the most cognitive domains, and the somatomotor, dorsal attention, and ventral attention networks were also implicated in multiple cognitive domains[209]. In general, more complex cognitive processes, such as reasoning and executive function, as well as social cognition, were associated with more networks[209].

Though relatively fewer studies have examined the neural correlates of social cognition in schizophrenia, there is considerable evidence for regional activation and functional connectivity abnormalities in relation to social cognitive deficits. Lower- and higher-level social cognition are believed to be subserved by partially dissociable but interacting networks in the brain[210-213]. Lower-level social cognition is thought to depend on a frontoparietal and insular "simulation network", including the inferior parietal lobule, inferior frontal gyrus[214,215], anterior cingulate cortex, and anterior insula[216,217]. Higher-level social cognition is thought to rely on a cortical midline and lateral temporal "mentalizing network", including the medial prefrontal cortex, temporoparietal

junction, and precuneus[218,219]. These lower- and higher-level social cognitive networks show overlap with the resting state frontoparietal and salience/ventral attention networks, and the DMN, respectively[220].

Meta-analyses of fMRI studies using emotion perception and theory of mind tasks in schizophrenia compared to healthy control groups have demonstrated altered brain activation in regions of the simulation and mentalizing networks[221-225]. Decreased activation in regions of the mentalizing network have also been identified in a meta-analysis of fMRI studies of theory of mind in individuals with CHR[226], though no differences in brain activation were found between at-risk and control groups in a recent meta-analysis of fMRI studies examining negative emotion perception[227].

Past work has identified associations between resting state connectivity among social cognitive regions and social cognitive performance outside the scanner in schizophrenia[168,228,229] and first-episode psychosis[230], as well as symptom severity in schizophrenia[231]. However, findings have been inconsistent, and such investigations lack insight into online social processing. Task-based fMRI studies have demonstrated greater functional connectivity in regions of the simulation and mentalizing networks during mentalizing in schizophrenia compared to healthy controls [232,233], though hypoconnectivity has also been reported between social cognitive regions during social processing tasks[234,235]. Such inconsistent findings are likely driven by case-control designs, often small samples, and varied analytical approaches. It should also be noted that conceptualizations of social cognition vary, and differences in the constructs being measured and reported domain scores may also contribute to variable results [236].

Studies in larger samples have used data-driven, computational approaches to elucidate the neural circuitry of social cognitive impairments. Associations between functional abnormalities in both the simulation and mentalizing networks and poorer social cognitive performance have been identified across individuals with schizophrenia and healthy controls during rest[237], a facial imitation task[21], and a more complex and naturalistic empathic accuracy task[24]. In particular, worse social cognitive performance has been linked to more distributed activation across the mentalizing and simulation networks[21], and greater intra- and inter-network connectivity across these social cognitive networks[24,237], indicative of decreased network efficiency and segregation. This work also suggests that neural activation patterns during social processing may relate to cognitive performance rather than diagnosis across schizophrenia and healthy controls. Evidence suggests that this pattern may exist transdiagnostically, across schizophrenia and autism for example[238].

Notably, both non-social[239] and social cognitive[186] domains have been proposed as candidate endophenotypes for schizophrenia. Given their associations with functional outcomes[174], they have also been identified as promising treatment targets. Accordingly, targeting brain circuitry important for these processes offers a potential novel therapeutic advance with implications for cognitive performance and, ultimately, functional outcomes[240].

fMRI IN RELATION TO TREATMENT: RESPONSE/RESISTANCE, MECHANISMS AND THERAPEUTIC TARGETING

Antipsychotic medication

Given that schizophrenia is likely a heterogeneous disorder involving multiple underlying pathological mechanisms[241], attempts to identify rational therapeutic targets have been challenging[242]. Functional brain imaging can be a powerful tool to better understand not only the underlying neural circuit dysfunction in schizophrenia, but how different interventions can modify these dysfunctional brain circuits. The incorporation of pre- and post-treatment fMRI in clinical trials offers an opportunity to investigate mechanisms of treatment response. Biologically based evidence can further support the efficacy of interventions in modifying brain function, and may provide evidence of "target engagement" even in cases where the clinical or functional outcomes are challenging to measure explicitly.

From 18 to 24% of patients with schizophrenia demonstrate complete treatment resistance from the first episode[243-245], and a similar percentage show only partial or inadequate response[246]. Ultimately, nearly 40% of patients are classified as non-responders to first-line antipsychotic medications, resulting in the overwhelming majority of health resource utilization associated with psychosis[247]. All effective and currently approved antipsychotic medications target dopamine D2 receptors, which are concentrated in the striatum[248,249]. A wide array of evidence is consistent with the hypothesis that there are two functional subtypes of schizophrenia with respect to treatment response: the hyperdopaminergic and normodopaminergic[250-252].

Cross-sectional[250] and prospective[253] PET studies suggest that elevated dopamine synthesis capacity in the striatum is characteristic of antipsychotic treatment responders, while treatment-resistant cases of schizophrenia have normal striatal dopamine functioning at baseline. Therefore, it is noteworthy that PET striatal dopamine synthesis capacity has recently been associated with differential patterns of cortico-striatal functional connectivity as measured by resting state fMRI[254,255]. However, striatal PET imaging may not be an easily translatable biomarker, since it is expensive, invasive, and involves exposure to ionizing radiation. Resting state functional connectivity is a promising neuroimaging technique to evaluate antipsychotic response. As resting state fMRI does not require an active task, it is especially practical in populations that may find traditional fMRI tasks difficult to perform[256]. Several investigators have used resting state functional connectivity of the striatum, a region rich in D2 receptors and the major site of antipsychotic action, to evaluate its potential to predict treatment response.

Evidence from several studies suggests that striatal circuits could be critical in mediating clinical response in people with psychosis. Resting state fMRI baseline striatal connectivity has been found to predict clinical response to antipsychotic treatment in a cohort of first-episode patients who had undergone no or minimal prior treatment[257]. This "striatal connectivity index" demonstrated 80%

sensitivity and 75% specificity for the prediction of acute antipsychotic response in an independent cohort of multi-episode patients. Confidence in these results was enhanced by independent data from a small longitudinally studied cohort of early-phase schizophrenia patients[258], in which antipsychotic treatment resulted in similar normalization of frontostriatal connectivity. Similarly, the role of baseline striatal connectivity in predicting treatment response in schizophrenia was supported by another study[259] in which greater hippocampal baseline connectivity followed by a connectivity increase over time to the caudate was associated with better response. Two recent prospective studies have produced comparable results[126,260].

Cross-validation of resting state functional connectivity patterns predictive of treatment response in patients with different clinical characteristics and environments is important to test the stability of the predictor. Accordingly, striatal resting state functional connectivity was explored in two cohorts of patients scanned on different MRI platforms: a cohort of medication-naïve first-episode patients and a cohort of unmedicated patients with schizophrenia[261]. In both cohorts, striatal resting state functional connectivity was predictive of subsequent treatment response to antipsychotic medication. Collectively, these independent and convergent replications suggest that striatal connectivity may be a critical mediator, and perhaps predictor, of antipsychotic drug effects on the brain.

Other functional networks have been studied in relation to their potential to predict antipsychotic treatment response. Functional connectivity of the DMN[262] has been investigated in the above mentioned two cohorts[261]. In both of them, resting state functional connectivity of the hippocampus, one of the principal regions of the DMN, was predictive of subsequent treatment response.

A recent systematic review and meta-analysis quantifying the utility of pre-treatment resting state fMRI in predicting antipsychotic response reviewed 22 datasets with 1,280 individuals, and concluded that striatal and DMN resting state functional connectivity were consistent predictors of antipsychotic treatment response[263]. The meta-analysis based on 12 datasets revealed an overall 81% sensitivity and 76% specificity to predict categorically defined treatment response.

Few studies have evaluated patterns of resting state functional connectivity in patients meeting criteria for treatment resistance, and differences in methodology have precluded meaningful conclusions[31]. More interesting are studies aimed to characterize patterns of resting state functional connectivity linked to the superior therapeutic action of clozapine in those not responding to trials of first-line antipsychotic medications. Because clozapine, unlike first-line antipsychotics, binds to dopamine D2 receptors with low affinity and has a uniquely rich pharmacology (with significant activity at other dopaminergic, muscarinic, adrenergic, histamine and serotonergic receptor subtypes[264-266]), distinctive resting state functional connectivity patterns associated with its efficacy should be expected. In treatment-refractory participants enrolled in a trial of clozapine, response to this drug was associated with an increase in corticostriatal resting state functional connectivity between the dorsal caudate and the frontoparietal network, which was also predictive of response at pre-treatment[267]. Although these findings need to be replicated with larger cohorts of treatment-refractory patients, they may indicate that changes in corticostriatal connectivity may represent a downstream mechanism of action common to all antipsychotic medications.

Another prospective neuroimaging study evaluated changes in clinical symptoms and patterns of resting state functional connectivity in schizophrenia patients who started treatment with clozapine[268]. A first step data-reduction of item-level clinical scales revealed four distinct patterns of treatment response to clozapine. Interestingly, those clinical patterns mapped onto distinct neuroimaging resting state functional connectivity features, that are thus relevant to clozapine-induced symptom change and can provide neuro-behavioral targets linked to clozapine efficacy.

Psychotherapy and psychosocial interventions

Though evidence is limited, fMRI studies have also shown that psychotherapy has the potential to induce functional brain changes in individuals with schizophrenia. For instance, cognitive behavioral therapy has been associated with increased functional connectivity between the DLPFC, dorsomedial prefrontal cortex and caudate[269], as well as between the DLPFC and amygdala/visual cortex[270], with prefrontal connectivity changes predicting long-term recovery[271].

Cognitive remediation and related psychosocial interventions have also been associated with increases in functional connectivity in frontal cortex[272] and increased frontal activation during task-based fMRI[273-275]. Activation in areas other than the frontal cortex have also been observed, including the anterior cingulate and parietal cortex[275,276]. Recent reviews investigating cognitive remediation in individuals with schizophrenia revealed positive associations between cognitive improvements and functional and structural changes in frontal brain regions[277,278]. Interestingly, a study examining changes in functional connectivity following cognitive remediation found that patients who received treatment showed more normalized brain network patterns, comparable to those observed in healthy controls[279]. Social cognitive training has also been shown to influence neural function in regions that support social cognition, such as the postcentral gyrus and amygdala, while improving emotion-processing abilities[280,281].

Studies in this field have usually included small patient samples, and additional research is required to comprehensively grasp the neural mechanisms involved in the effects of psychotherapy and psychosocial interventions, further explore ways to optimize them for improved functional outcomes, and demonstrate if such changes are transitory or persist over time.

Neurostimulation

A variety of neurostimulation methods have been used to treat schizophrenia, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct

current stimulation (tDCS), and deep brain stimulation (DBS).

ECT is being used in treatment-resistant schizophrenia or as augmentation in clozapine-resistant patients[283,284]. Baseline fMRI imaging has revealed patterns of dyssynchronous dynamic connectivity involving prefrontal-temporal regions as a prognostic marker of response to ECT[285]. Following ECT, a decreased coupling between the right amygdala and the left hippocampus, and an increased functional connectivity between the hippocampus and a range of cortical regions, have been reported[286,287].

rTMS and TDCS are becoming significant tools for addressing symptoms of schizophrenia that are not mitigated by conventional treatments[288], such as cognitive impairments[289,290], negative symptoms[291,292], and refractory hallucinations[293-295]. Early rTMS targets were identified via local changes in brain activity[296,297]. However, fMRI research has demonstrated that rTMS exerts deeper and broader effects by propagating along neural networks connected to the target site[298-303].

fMRI-guided rTMS targeting has been used for refractory auditory hallucinations. Several studies have targeted the temporoparietal junction, generally using an "inhibitory" protocol[293-295], as it represents a core region of overactivity within neural circuits associated with hallucinations[304]. Studies examining post-treatment changes found increased network connectivity in regions of the auditory/sensorimotor, central executive, and default mode networks[305], and normalized connectivity between the default mode and language networks, and within the auditory and central executive networks[306]. Another protocol using "excitatory" rTMS, with a functionally identified target in the language region of the superior temporal sulcus, observed a decrease in hallucinations[307].

Additional studies have shown both a reduction in activation after rTMS delivery to the temporal lobe and a corresponding decrease in hallucinations[308]. Moreover, a unique fMRI-based case study has suggested that there may be efficacy for hallucinations in very late onset schizophrenia via theta-burst stimulation (TBS)[309]. However, a recent meta-analysis did not find strong evidence for a reduction in hallucinations following rTMS or tDCS [293].

Neurostimulation to reduce negative symptoms has targeted the DLPFC[292], based largely on early neuroimaging work implicating the prefrontal cortex in schizophrenia and negative symptoms[310,311] and the antidepressant effects of rTMS to the DLPFC[312]. While fewer studies have used neuroimaging to assess the mechanistic effects of rTMS for negative symptoms, task-induced activity in the DLPFC has been shown to increase[313], and left DLPFC stimulation has been associated with a decrease in negative symptoms and a corresponding change in dynamic connectivity of the cortico-thalamo-cerebellar circuit[314]. Similarly, reduced negative symptoms and large-scale modulation of functional interactions have been noted with intermittent TBS of the left DLPFC[315]. Related studies focused on social cognitive deficits support modulation of neural circuitry during social-emotional evaluation with rTMS to the DLPFC[316].

Two potentially powerful ways by which evolving fMRI approaches can improve rTMS is the identification of novel circuit-based targets and personalizing treatment. As an example of the former, a data-driven analysis identified connectivity between the DLPFC and the cerebellar vermis as the most significant predictor of negative symptom severity in a sample of people with schizophrenia, and validated this in an independent sample by demonstrating a relationship between increased DLPFC-cerebellar connectivity and reduction in negative symptoms after rTMS to the cerebellar vermis[166]. This aligns with evidence suggesting that individual variability in functional connectivity can affect response to brain stimulation. Indeed, reductions in depression following DLPFC stimulation have been associated with anticorrelation (i.e., negative correlation) of the rTMS sites with the subgenual cingulate cortex[317]. The proximity of the rTMS target to an individually calculated optimal target based on anticorrelation with the subgenual cingulate cortex has also been found to predict treatment response in depression[318,319], raising the possibility that individualized rTMS targeting may improve treatment outcomes[33]. The combination of personalized functional connectivity mapping to identify target locations, and electric field modeling to maximally stimulate critical regions, may individually optimize neurostimulation treatment[320] and be applicable to novel treatment targets in schizophrenia, such as social cognition[32].

Findings in schizophrenia with tDCS, a more portable method for neurostimulation, have also been examined in relation to fMRI, but data are preliminary. Functional connectivity of the superior temporal gyrus has been suggested as a potential prognostic marker for response to tDCS[321]. Separate studies focused on cognition have reported positive effects with tDCS in schizophrenia and associated changes in neural circuitry[322]. Negative symptoms have also been targeted by tDCS, showing reductions in symptom ratings and associated prefrontal circuitry changes[323,324].

DBS is an invasive surgical treatment based on implantation of a small electrode capable of modulating localized aberrant neural circuits[325,326]. The largest human trial to date in schizophrenia included only seven participants, four of whom showed significant reductions in symptoms with electrodes placed in the subgenual anterior cingulate cortex or the nucleus accumbens[327], based in part on prior success for these regions in depression[328] and obsessive-compulsive disorder[329]. A single case study of DBS in the substantia nigra showed clinical improvements, including a complete cessation of hallucinations[330].

DBS within schizophrenia has faced several challenges, including difficulty or failure recruiting participants[331], ethical considerations around vulnerability[332], and concerns about increased surgical risks in people with this disorder[333,334]. It is, therefore, critical that future DBS trials are informed by a deeper understanding of the neural circuitry of the specific symptoms or behaviors being targeted, or systems which might have broader impact. Ideally, such targets should be established at the individual level, to optimize treatment outcomes.

Functional imaging can also identify broader mechanisms of psychosis to provide targets for novel interventions. As mentioned, there is substantial evidence supporting a disturbance in thalamo-cortical and thalamo-striatal connectivity in schizophrenia, which has been suggested as a crucial system that contributes to a wide range of underlying cognitive deficits and clinical symp-

toms[335,336]. The thalamus includes multiple nuclei that interact with subcortical and cortical regions[337-339], modulating cortical connectivity and maintaining or coordinating task-relevant cortical representations[340]. Interestingly, lesions to associative thalamic nuclei can result in psychosis symptoms[341]. Targeting specific thalamic nuclei may provide an opportunity for broad clinical impact. Emerging treatment modalities such as focused ultrasound, allowing deep brain neuromodulation of specific brain regions[342], may provide a novel mechanism to modulate thalamic connectivity and function to treat schizophrenia.

fMRI AND DATA-DRIVEN APPROACHES TO DISSECT HETEROGENEITY

High levels of heterogeneity of brain metrics is the norm, even in non-clinical populations[19,37]. A growing body of evidence suggests that schizophrenia encompasses even greater variability in both fMRI task activation[17,18,343] and resting state functional connectivity[344-346] than is present in the general population. Recent work has shown that there is minimal overlap in brain abnormalities among those who share the same diagnosis, indicating that differences at the group level may conceal biological heterogeneity and interindividual variations among people with schizophrenia[26]. Consequently, relying exclusively on case-control research will be inadequate to advance efforts for clinical translation of neuroscience results.

The Research Domain Criteria (RDoC) initiative shifts away from the conventional case-control research model, calling for integration of multi-level data (e.g., deep phenotyping across measures of genes, circuits, physiology, cognition and behavior) to characterize the full range of transdiagnostic brain-behavior dimensions within and across domains[47,347]. European initiatives – e.g., the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project – have similarly called for a shift to transdiagnostic research[348]. The ultimate aim is to identify subsets of individuals with more homogeneous biological profiles that map onto specific clinical features, which may inform stratification for clinical trials and biologically targeted transdiagnostic treatment approaches. Both dimensional brain-behavior research approaches and biotyping approaches align with this framework.

The neural circuitry of specific symptom, behavioral or cognitive domains can be mapped via brain-behavior associations, often assessed using linear models. Such approaches have been used to map the underlying neurobiology of symptom profiles (e.g., negative symptoms[166,167], hallucinations[304]), identify targets for brain stimulation[166], and predict clinical outcomes and medication response[349,350]. Utilizing linear analysis can delineate variability which exists across a given population, as opposed to relationships which are driven by a particular disorder. For example, case-control research has indicated that disruptions in social cognition in schizophrenia[173,187] are linked to differences in social cognitive neural circuit activation[223]. However, when examining the relationship between social cognition and related circuits across schizophrenia and controls, social cognitive network connectivity was associated with social cognitive deficits but not diagnosis[24].

Biotyping is another approach to tackling the challenge of heterogeneity[28,29,348], wherein data-driven methods, such as clustering, are used to identify subgroups with common neurobiological characteristics. Subgroups with shared brain-behavior relationships may be more homogeneous in therapeutic response and etiology[351,352]. Indeed, transdiagnostic work has identified subgroups with shared patterns of brain activation[21], functional connectivity[230], gray and white matter structure[353,354], and other multivariate biomarkers[355], which may have implications for prognosis and targeted treatment development. However, clustering approaches can, at times, separate participants into discrete groupings even when they exist along an underlying continuum[19,356].

Multimodal fusion techniques such as similarity network fusion[357] – which can integrate different data types and identify individuals with similar profiles across clinical/behavioral, structural and functional neuroimaging, and other metrics (e.g., genetics, peripheral biomarkers) – may prove a powerful tool for dissecting heterogeneity and deriving reliable biotypes. For example, fusion across structural imaging and behavioral measures in people with schizophrenia, autism and bipolar disorder identified novel, reliable and separable biotypes with distinct neural circuit-cognitive profiles, whereby effect sizes for between-group differences were greater with data-driven subgroups than those found using conventional diagnostic groupings[354].

Advanced analytical approaches such as multivariate statistics may allow for the identification of unique and common neural circuitry underlying clinical/behavioral scores[41,43]. Multivariate approaches can also provide insight into which behavioral domains represent shared constructs of underlying risk factors with common neurobiology[358], case-control differences during cognitive processing[233,359,360], or differences across genotypes[361]. In this way, neurobiology can inform the understanding of clinical domains[27]. Likewise, multivariate approaches can identify common and distinct neurobiological markers and behaviors across related sets of psychiatric disorders[362].

As previously described, recent shifts in research frameworks have also led to the use of predictive multivariate machine learning techniques, moving from explanatory to predictive analyses[7,363]. Machine learning techniques are ideally suited for making predictions from neuroimaging data, given that they are designed for multivariate analyses of high-dimensional data[364]. Machine learning models using fMRI data have been utilized to make binary classifications[365,366], and regression-based prediction approaches are becoming increasingly popular to make individual-level predictions of behavior, clinical symptoms, and functioning[367], or examine deviations from a normative distribution[368]. Generalizability of machine learning models established on the basis of a given sample can be evaluated using simulations that resample data, such as bootstrapping and cross-validation, but should ideally involve applying the model in a new external validation sample[30,369].

Machine learning has also been used to provide more individualized parcellation of brain regions on a common template, improving the predictive power of functional connectivity[370]. In-

dividualized deviations from common group parcellations using support vector regression have been related to both positive and negative symptoms, in contrast to atlas-based connectivity[371]. Ideally, future applications of machine learning to predict behavior or cognition at the individual level[372] may serve to inform clinician decisions.

The use of functional connectivity data in association with other modalities (neuroimaging, genetic, electrophysiological) to improve prediction performance also holds great promise. However, its implementation will necessitate building models which use carefully selected predictors, and testing their accuracy, generalizability and clinical utility in real-world clinical settings[373].

Prediction of treatment response at the individual patient level will also be of great value. For example, using machine learning algorithms and the resting state functional connectivity of the superior temporal cortex, medication-naïve first-episode psychosis was identified with an accuracy of 78.6%, and treatment response at the individual level was predicted with an accuracy of 82.5% [374].

METHODOLOGICAL CONSIDERATIONS AND ADVANCES

A common refrain in neuroimaging is the need for larger, representative studies. An underpowered study reduces the true positive rate for significant findings in the usual null-hypothesis framework, making reproducibility of any findings an overarching concern. Consortia of researchers to address the need for larger, more representative datasets are needed in neuroimaging just as they are in clinical trials[11].

The consortia approach can allow to collect large samples, as in the Function Biomedical Informatics Research Network (FBIRN), the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP), the Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS), the NAPLS and the ProNET studies, and the ongoing Accelerating Medicines Partnership (AMP) - Schizophrenia (SCZ) Programme[375-379]. In these projects, the focus is making the study parameters as similar as possible, so that the samples are homogeneous, the clinical assessments are the same across the whole sample, and the imaging techniques are prescribed prior to data collection to reduce site differences. This can increase power by reducing heterogeneity. Other consortia work with already-collected data[13]: the prospective meta-analysis technique used by the ENIGMA Schizophrenia Working Group, for example[12], prescribes the imaging processing techniques to be applied across dozens of datasets, removing the data processing and analysis as a source of heterogeneity. This kind of approach can lead to *post-hoc* datasets of thousands or tens of thousands.

The power of large samples is key, with international representation and increased inclusivity, but it also leads to innovative approaches for identifying and addressing heterogeneity. How much of the variability in published results is due to differences in the statistical approach, or to differences in characteristics of the sample? For example, in the meta-analysis of subcortical volumes in the ENIGMA Schizophrenia Working Group[12], a moderation analysis demonstrated that hippocampal volume deficits were more severe in samples with a higher proportion of unmedicated patients, adding to our understanding of sources of heterogeneity. At the same time, the drive to combine datasets directly, rather than doing a meta-analysis, has led to applications to fMRI measures of harmonization techniques known as ComBat (named for "combating batch effects when combining batches"), borrowed from genetics, with notable successes[381]. Standardized pipelines to reduce sources of noise while being sensitive to individual variation are becoming the norm, improving the chances for reproducible results[39].

As previously noted, recent advancements in MRI research approaches have opened new opportunities to address individual heterogeneity, collectively called precision fMRI. First, advances have been made in imaging sequences on MRI scanners. Hyperband fMRI can improve image quality via higher spatial and temporal resolution[34]. In addition, multi-echo fMRI images might be less susceptible to the effects of human motion[35]. Second, novel "personalized" MRI data processing approaches can better account for individual variability in brain morphology. Using cortical surface-based fMRI pipelines to account for differences in folding patterns across individuals will increase the power to detect clinically relevant effects.

Furthermore, fMRI data can map individual functional topography[44,370,382], which can provide additional advantages for finding associations with symptoms[371] or cognition[383]. Mapping individual functional topography requires more prolonged and more frequent within-individual scans[51], and is therefore mostly conducted in studies where multiple MRI sessions are available, but can build a more reliable, stable and individually specific "functional connectome"[37,50,384].

When planning the next generation of fMRI research experiments, one additional consideration will be what participants will do inside the scanner. Participants could be asked to complete any number of cognitive tasks (task-based fMRI), they could watch movies (sometimes referred to as "naturalistic viewing"[385]), or lie still (i.e., resting state fMRI). Resting state fMRI has the advantages of not needing additional equipment and having simpler task instructions that can still be followed when participants have more severe symptoms or cognitive deficits. However, the "resting state" is also less engaging, and so participants are more likely to move[386] and fall asleep[387] than when a task or movie is present. While much of the original work with task-based fMRI involved fitting a task model to the fMRI data (i.e., region-based analysis), it is crucial to consider that analytic tools that were primarily developed for resting state fMRI – that is, the calculation of functional connectivity and network-based modelling – are equally, if not more, useful when applied to task-based or naturalistic viewing data.

Task-based and resting state functional connectivity could lead to different biomarkers due to different "brain states". Examining connectivity during task states provides additional information on the relationship between connectivity and cognition[20,388]. Therefore, renewed interest in functional connectivity during different brain states is emerging, with some newer tasks being

developed to study paranoia[389]. Considering both resting state and task-based functional connectivity is essential to enhance interpretability and sensitivity to brain-behavior relationships [24,237].

LIMITATIONS

Although fMRI has been highly impactful in psychiatry research in the past three decades, it is associated with several kinds of limitations which have until now hampered its deployment in clinical settings. If fMRI is to become a useful diagnostic/prognostic tool in the care of patients with schizophrenia – e.g., to predict conversion to psychosis from at-risk states, to predict response to certain antipsychotic medications, or to guide precision treatment – these limitations will need to be overcome.

We divide these limitations into three categories: technical, experimental and conceptual. Technical limitations are those concerning data collection and analysis. Experimental limitations are those that come up in the conduct of clinical fMRI research, such as sample size and power limitations, and sampling biases. Conceptual limitations refer to issues in interpretation of fMRI findings in clinical schizophrenia research. This survey of limitations helps provide a realistic assessment of the current state of the field.

While fMRI has provided valuable insights into the pathophysiology of schizophrenia, it is important to keep in mind what it is measuring. fMRI is an indirect measure of brain activity. It is not able to delineate activity differences across neurotransmitter systems, which would help identify putative pharmacological targets. The spatial resolution of fMRI is closely associated with the signal-to-noise ratio, and influenced by field strength, brain coverage, acquisition technique, and temporal resolution[390]. The temporal resolution of fMRI is limited by the hemodynamic response time, and the BOLD response peaks about 5-6 seconds after stimulus onset, which is much slower than the neural response. However, early work revealed that jittering stimuli presentation and the use of event-related designs could help to overcome these obstacles [391,392], and there is increasing evidence to suggest that early phases of the BOLD response may provide information about neural activity with higher temporal resolution[393].

Recent advances in echo planar imaging (EPI) acquisition have allowed for increased spatial and temporal resolution. Multi-band accelerated EPI (also known as hyper-band), popularized and made readily available by the Human Connectome Project[34,394], allows for the collection of multiple brain slices simultaneously, increasing the speed of whole brain coverage and spatial resolution[395-397]. Ultra-high magnetic fields improve the signal-to-noise ratio and enhance the BOLD contrast, allowing for greater spatial resolution, and are becoming more commonly used in schizophrenia research[398], but high-field fMRI has its own technical and methodological challenges and is not widely available[399].

fMRI is sensitive to a variety of noise sources, including scanner artefacts, participant motion, and cardiac and respiratory activity. Technological improvements have helped to mitigate motion artefacts: accelerated imaging reduces the opportunity for participants to move, but increased resolution also heightens sensitivity to participant motion[400]. Improved scanner hardware has resulted in reduced signal distortion, blurring and dropout[394,401].

Evidence suggests that multi-echo fMRI may provide a promising avenue for mitigating motion artefacts[35,402]. Multi-echo reads fMRI data at multiple time points for each slice acquisition, removing non-BOLD signal (such as scanner and motion artefacts). It has also been shown to allow greater reliability in shorter scan durations[403], which may be critical to implement functional imaging in clinical samples. However, while software tools for multi-echo analysis exist[404], multi-echo sequences are not available on all MRIs, and require higher technical knowledge to implement and analyze. The influence of motion on fMRI metrics remains a prominent concern in studies of functional connectivity[405], particularly as clinical populations such as people with schizophrenia frequently show greater in-scanner motion[406-408].

Despite hardware improvements, residual sources of noise and artefact are inescapable in any imaging technology, and must be addressed in the image reconstruction and data analytic process. Pipelines for modelling and removing physiological noise and participant motion have been widely utilized to mitigate these effects[409-412]. For example, global signal regression (GSR) is a potentially powerful denoising strategy[413] which is effective at minimizing associations between motion and connectivity in resting state fMRI data[411,412]. However, it has the potential to remove signals of interest[414], introduce spurious anticorrelations[415], and distort group differences[416,417]. There is also some evidence to suggest that the global signal differs in people with schizophrenia compared to healthy controls[418,419]. Thus, while GSR may mitigate multiple noise sources, it has the potential to remove important signal characteristics, and many publications present dual sets of results (both with and without GSR), without making claims as to which represents the "ground truth"[420].

More broadly, the sheer multiplicity of analytic choices required in fMRI research – from raw signal to processed images and then to statistical brain-behavior relationships and group comparisons – vastly increases the number of "researcher degrees of freedom"[421], thereby increasing the possibility of false positives and non-replicability. Additionally, the three most widely utilized software packages for analyzing fMRI data have subtle differences in implementation of basic pre-processing and analytic steps[422], potentially yielding different results even under similar assumptions. Moreover, these software differences can have varying effects on output across different task conditions[423], software versions[424], or even different hardware configurations and operating systems[425].

A recent landmark study[40] illustrated the magnitude of the challenge in generating reproducible results in fMRI studies. A single fMRI dataset was distributed to 70 independent research teams, along with a pre-specified set of hypotheses to test, resulting in three key findings: a) no two groups utilized the same processing pipeline; b) the degree of concordance across groups was approximately midway between pure chance and complete agreement; and c) the researchers were generally inaccurate in their predictions about the results, with an "optimistic" bias to-

wards expecting significant results.

Due to increasing awareness of these issues, at least three sets of solutions have been proposed for future research: a) the use of stable, uniform and openly-annotated pipelines and platforms[426-430]; b) benchmarking approaches to quantifying and reporting the residual degree of artefact and variability present in a given set of outputs[431-434]; and c) performing "multiverse" analysis, which entails reporting results from a multiplicity of analytic approaches within a single paper[435,436].

Experimental limitations, including small sample sizes and sampling bias, have also contributed to reproducibility and generalizability issues in fMRI research, as has variability across studies in participant sampling. As previously described, participant heterogeneity, the use of small samples, and focus on case-control comparisons have contributed to inconsistent findings in the field and impeded biomarker identification, but the shift towards larger, multi-site samples, deep phenotyping, and dimensional vs. categorical approaches holds considerable promise.

Though it is a non-invasive technique, fMRI requires participants to remain still and supine, often for an extended period of time, within a noisy, confined space, inherently limiting the potential sampling pool. A recent study found lower trait anxiety scores in healthy fMRI study participants across multiple centers, indicative of sampling or self-selection bias[437]. These could result in failure to generalize across study contexts and the full range of the population.

As mentioned, greater in-scanner head motion has been reported in clinical populations[406-408]. fMRI in-scanner head motion has been associated with cognitive performance[438] and IQ[439]. Accordingly, there is evidence that participants with greater cognitive and functional impairment tend to be more often excluded through quality control procedures[440], precluding the analysis of data from those who may be the most in need of interventions.

In clinical studies, unstable illness and comorbidities are often exclusion criteria. It is challenging to study inpatients, and even more difficult to include those who are so ill as to require substitute decision making. Many patients use substances and are often excluded from research, because these substances may act on the same systems as the illness itself[441,442]. The effects of antipsychotic medication on the brain are also not yet fully understood[443,444], often acting as a confound in studies including medicated patients[445]. This limits the generalizability of most fMRI studies. Moreover, the validity of selected cognitive and clinical assessments, either in or out of the scanner, is another critical consideration that can influence the reliability of brain-behavior associations[446]. fMRI is also expensive and not necessarily readily available in lower-income and more rural areas, and its potential clinical utility is influenced by and must be weighed against these factors.

In addition to these technical and experimental issues, the field is also increasingly grappling with challenges to the conceptual framework underpinning much conventional neuroimaging research to date. As previously highlighted, most fMRI studies examine functional connectivity differences between cases and controls, but functional connectivity across the brain is a multifaceted phenomenon that may be, to some extent, a "moving target". While some of its aspects are consistent for an individual across time and condition, other components are not highly reliable across testing sessions[447]. Specifically, individual connections (edges) demonstrate a "poor" reliability (average intraclass correlation coefficient = 0.29), while large within-network functional connectivity values are more stable[448]. Moreover, functional connectivity changes dynamically within a scanning session[449], and this dynamic variability is itself a heritable phenomenon that may influence cognitive and psychiatric traits[450].

Additionally, while functional connectivity has traditionally been measured using canonical boundaries for nodal regions (albeit with varying degrees of spatial resolution), there has been a recently emerging trend towards individualized definition of functional connectivity network boundaries[20,37,44,451-453], following demonstrations that these individual differences are heritable[454], increase statistical strength of brain-behavior associations[48,383,455], and are relevant to the study of psychopathology, including schizophrenia[36,456].

Similarly, fMRI studies of task activations generally share the implicit assumption that there is a single region, or set of regions, underlying a given functional process (e.g., memory or response inhibition). However, it has long been acknowledged that the human brain can meet a given set of task demands using different strategies[457,458]. Consequently, it has recently been suggested that a "complexity" approach to brain-behavior relationships, allowing a many-to-one mapping of brain states to behavior, will be more productive than comparing groups on single-region activations[459]. This approach is congruent with the recent search for subgroups of patients that share a similar "biotype" – i.e., the pattern of overall brain organization may identify subgroups of patients with distinct pathophysiology[355,460-463]. It is also important to note that non-canonical functional network patterns may be marked by relevant demographic and clinical differences that should not be ignored[464]. These recent changes to the underlying conceptual framework of fMRI studies in schizophrenia are discussed in greater detail in the section below.

FUTURE DIRECTIONS

Within each section of this paper, the evolution of approaches, techniques and strategies of fMRI research in schizophrenia has been reviewed (see Table 1 for a summary). For example, initial studies started with small sample sizes comparing chronic patients to healthy controls. By contrast, current studies more commonly include people in the earlier stages of illness (including CHR subjects) and may employ large consortium-based approaches to enhance sample size. The sections of this paper themselves have a historical arc, starting with diagnostic case-control approaches to identify group differences, moving to more recent efforts to use fMRI for personalized treatment in a precision medicine paradigm, such as individually-targeted neurostimulation. This final section serves to bring together aspects of each of the preceding sections, with a view to the future.

Table 1 Summary of functional magnetic resonance imaging (fMRI) research on schizophrenia

	Advances	Challenges
Diagnostic markers	Functional neuroimaging analyses have evolved from regional approaches to global connectivity, including advanced analyses to characterize key pathophysiologic markers of schizophrenia and clinical high risk more comprehensively. Machine learning approaches hold promise for parsing heterogeneity and predicting conversion from clinical high risk to psychosis.	Despite an abundance of fMRI-based case-control differences, findings are inconsistent, and the search for clinically useful functional imaging markers of schizophrenia continues. Heterogeneity across people with schizophrenia and healthy controls may impede diagnostic biomarker discovery, and small, single-site samples limit generalizability.
Markers of negative symptoms	Potential neural markers of negative symptoms have been identified in fMRI studies of early and chronic schizophrenia, and results suggest that these may vary by symptom construct, highlighting the importance of symptom delineation when investigating their neural basis.	Negative symptoms are a major determinant of poor functional outcomes in schizophrenia which lack effective treatments, yet few functional neuroimaging studies have focused on them, and different conceptualizations of negative symptoms may obscure results.
Markers of cognitive deficits	Particular neural networks have been implicated in non-social and social cognitive deficits in schizophrenia, with recent dimensional analyses suggesting that neural activation patterns during cognitive processing may relate to cognitive performance rather than diagnosis across schizophrenia and healthy controls.	Inconsistencies in functional neural correlates of cognitive performance are likely due, in part, to variability in cognitive abilities, and how they are conceptualized and measured.
fMRI in relation to treatment: response/ resistance, mechanisms, and therapeutic targeting	fMRI has provided insights into potential treatment response markers and mechanisms through pre- and post-intervention analyses of antipsychotics, psychotherapy and psychosocial interventions, and neurostimulation. For instance, striatal resting state functional connectivity has emerged as a potential marker for antipsychotic treatment response. The use of functional imaging to guide neurostimulation treatments – such as DBS, rTMS and tDCS – allows for more precise targeting of symptom-related circuits, and recent advances in individualized targeting may optimize target engagement and treatment response.	The mechanisms of many therapeutic agents in schizophrenia are poorly understood. The identification of therapeutic targets has been hampered by symptom heterogeneity likely involving multiple underlying pathological mechanisms and contributing to variable response rates.
fMRI and data-driven approaches to dissect heterogeneity	Heterogeneity in schizophrenia may be better characterized using dimensional or more individualized rather than categorical approaches, including linear models for mapping brain-behavior associations, biotyping through data-driven clustering, and advanced multivariate techniques to identify distinct and shared neural features with other psychiatric disorders.	It is unclear how to best quantify or classify heterogeneity (e.g., biotypes versus dimensional approaches), and translate heterogeneous results to clinical practice.
Methodological considerations and advances	Collaborative research and consortia approaches have facilitated the aggregation of large and diverse neuroimaging datasets and shared analytical pipelines, offering international representation, enhanced statistical power, and standardization, as well as improved reliability and generalizability. Improved imaging sequences, personalized data processing approaches, and mapping individual functional topography via deep phenotyping offer opportunities to address individual heterogeneity using precision fMRI.	Refined measurement techniques are required to capture individual variability in brain organization and connectivity profiles, as well as changes in state-related brain signatures.

DBS – deep brain stimulation, rTMS – repetitive transcranial magnetic stimulation, tDCS – transcranial direct current stimulation

In the diagnostics arena, initial enthusiasm was generated by small sample size studies showing apparently clear differences between patients and non-psychiatric controls using fMRI. For example, several studies demonstrated reduced prefrontal activation in people with schizophrenia on the "N-back task" of working memory[465]. However, conceptual issues related to heterogeneity were apparent even in these early studies, some of which demonstrated increased prefrontal activation, attributed to "cortical inefficiency", such that patients might use greater prefrontal resources even while achieving lower accuracy[466]. Of note, as early as 1998[197], with very small sample sizes, individual level maps of activation were examined, and the authors concluded: "Five of six patients, including two who were neuroleptic-naïve, failed to activate DLPFC. In addition, a tendency for overactivation of parietal cortex was seen". While the authors attributed much of this variability to motion (which in part was likely correct), they were prescient insofar as no one patient uses exactly the same set of voxels (brain regions/circuits) to perform a task in the scanner[459]. These observations were not followed up for nearly 20 years, as the template for the vast majority of studies was a case-control comparison, followed in some cases by conducting a brain-behavior correlation with task performance for regions showing between-group differences. Work emerging over the past five years has substantially changed the way we think about heterogeneity in brain activation and network connectivity patterns across individuals, providing a potential roadmap forward.

With larger sample sizes and data-driven statistical approaches, it has become increasingly clear that there are relatively distinct patterns of activation amongst subgroups of patients. At the same time, these patterns may not differ when taking patients with schizophrenia and comparing them to non-psychiatric controls, or to other diagnostic groups, such as bipolar disorder. For

instance, in tasks related to social cognition, data-driven analyses aimed at heterogeneity dissection showed that subgroups of patients used different brain areas (and potentially neural strategies) to complete the same facial emotion imitation task in the scanner[21]. However, non-psychiatric controls also used the same range of networks/strategies, and there was no difference in the frequency of patients or non-psychiatric controls in each strategy-defined group. Nevertheless, there was a relationship between strategy/network utilization and social cognitive performance, such that participants in the "deactivating" group demonstrated better performance relative to people in the "hyperactivating" and "intermediate" groups. Additional investigations in larger samples (e.g., from the Human Connectome Project) show that the relationship between task-related fMRI network utilization and behavioral performance across a variety of cognitive tasks may fall along dimensions[19]. However, the dimensional position of any individual participant may vary as a function of task.

Does this mean that between-group (i.e., schizophrenia versus non-psychiatric control) comparisons are uninformative? Recent data suggest that with large enough sample sizes, collected from multiple centers, certain findings of small effect are reliable. For example, using resting state fMRI, it does appear that cortico-striato-thalamo-cortical network differences are present when comparing patients with schizophrenia to controls[126]. At the same time, there is individual variability within each group, and accounting for personalized intrinsic network topography can strengthen results[44]. It is also likely that the robustness of these findings can be increased by using higher quality fMRI acquisitions (e.g., multi-echo fMRI) of longer duration. Indeed, repeated acquisitions may be of highest value to obtain more precise functional mapping at the individual level. Specifically, just 10 minutes of multi-echo data using a repeated within-person longitudinal design yielded better test-retest reliability than 30 minutes of single-echo data in independent datasets[403].

The collection of very large sample sizes (in the thousands) to conduct cross-sectional group-wise or brain-behavior correlational analyses is very expensive and may only yield very small effect sizes[49]. Moreover, the findings of such studies are not applicable at the individual patient level. Thus, rather than a study of 1,000 patients scanned once, it may be more fruitful to conduct a study of 100 patients scanned 10 times each. Longitudinal studies may yield substantially greater effect sizes than a cross-sectional approach. In fact, a recent meta-analysis showed that effect sizes may be 290% greater in longitudinal studies[467]. At the individual level, data aiming to identify personalized signatures of brain function show that even six scans may be sufficient to robustly identify each person[468].

Such longitudinal approaches may also provide the opportunity to address important clinical questions in the treatment of schizophrenia, aligning with the precision medicine method that has been successful in specialties outside of psychiatry. One urgent clinical question in the treatment of schizophrenia is prognosis – patient outcomes are highly variable, and up to 40% of patients are ultimately classified as treatment resistant. Relatedly, it is of particular interest whether fMRI measures can capture the likelihood that a given patient will respond to conventional treatments, or will require clozapine. In short-term clinical trials, or in observational studies examining longer-term clinical, cognitive or functioning trajectories, study visits can be paired with an MRI scan. Importantly, this may not be an infinite requirement. It is plausible that a finite number of functional brain map trajectories correspond to specific clinical trajectories, or to treatment response profiles. If a large-scale prospective study can identify these profiles, subsequent clinical studies might require only one or two scans to determine a patient's trajectory, potentially informing clinical decisions. In early stage psychosis, for instance, some patients quickly improve and are able to resume work or school, while others struggle considerably, may be re-hospitalized, or require more intensive wrap-around care. Having this information within the first few weeks of care in an early psychosis program would allow for more efficient use of finite resources for those patients who require it most.

Remaining at the individual level, knowledge of the specific set of networks that a patient used during a task, or his/her individualized functional connectivity profile, can serve as essential information for targeting neurostimulation. For example, more personalized targets are associated with greater improvement in memory performance[299,469] and depressive symptoms[319]. Therefore, targeting toward a group mean of peak connectivity may result in maximal treatment efficacy for a subset of individuals, but will miss the optimal target for a substantial number of other individuals. Currently funded clinical trials are seeking to determine if fMRI can be clinically useful in order to improve targeting of neurostimulation treatment aimed at cognitive performance, negative symptoms and/or depressive symptoms in people with schizophrenia. If shown to be useful, personally-refined, image-guided interventional psychiatry may become a reality, blending precision medicine and personalized medicine into one[32].

However, if the field increasingly moves towards individualized approaches, it is incumbent upon us to be conscientious and equitable in terms of which individuals we study. Currently, several groups of patients with schizophrenia are under-represented in fMRI studies. The most ill patients, some of whom are not able to provide informed consent, are greatly under-represented in research. Ethics committees, patient advocates, clinicians and researchers must collaborate to change this. In other fields of medicine, those in the most need often participate in clinical trials. Additionally, women are under-represented in schizophrenia research[470], partially due to differences in prevalence and sex-based variability in illness severity. However, women's health research is underfunded in general[471], and a greater effort must be made to include women with schizophrenia in fMRI research, and particularly in clinical trials employing fMRI. Moreover, people of minoritized ethno-racial backgrounds are under-represented in this research[472]. Encouragingly, funders are making efforts to provide and promote opportunities for more inclusive research, and requiring justifications regarding sample recruitment related both to ethno-racial diversity and sex/gender diversity. Finally, diversity in age is required in our samples: for example, adolescents at risk for schizophrenia may have a functional signature

that changes across the lifespan.

The ultimate question is whether fMRI can be clinically useful in the care of patients with schizophrenia. Early clinical guidelines suggested that neuroimaging should be part of routine practice in a first episode of psychosis, in order to identify possible "organic" causes. However, any advantage of fMRI is largely unrelated to rare, potentially identifiable causes of psychosis. Instead, fMRI research should address potentially actionable clinical decisions that are routine in schizophrenia treatment – i.e., which medication should be prescribed if an fMRI scan shows a signature of treatment resistance to conventional antipsychotics, or whether a given patient is likely to have persistent functional impairment based on early neuroimaging data, thus requiring display of significant psychosocial resources. In such cases, the economic cost of fMRI, and in some cases the challenge of travel to a center for a patient living in a more remote area, may be worth it. Future evaluations of the utility of fMRI in prognostic and treatment response studies may consider including a health economics analysis to make a tangible clinical impact.

ACKNOWLEDGEMENTS

A.N. Voineskos is funded by the US National Institute of Mental Health (NIMH), the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation, the National Sciences and Engineering Research Council of Canada, the Centre for Addiction and Mental Health (CAMH) Foundation, and the University of Toronto; C. Hawco by the NIMH, the CIHR and the CAMH Foundation; N.H. Neufeld by the Brain and Behavior Research Foundation (BBRF), the CIHR, the Physicians' Services Incorporated Foundation, the Labatt Family Network for Research on the Biology of Depression, the University of Toronto, and the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario; S.H. Ameis by the NIMH, the CIHR, the University of Toronto, Autism Speaks Canada, and the CAMH Foundation; A. Anticevic by the US National Institutes of Health, and the Simons Foundation Autism Research Initiative; E.W. Dickie by the BBRF, the NIMH, the CIHR and the CAMH Foundation; J. Gallucci by the University of Toronto; K. Cadenhead, J.A. Turner, A. Lahti, A.K. Malhotra, D. Öngür, T. Lencz and D.K. Sarpal by the NIMH; L.D. Oliver by the BBRF.

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DOI:10.1002/wps.21159