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Resting-State Networks in Schizophrenia

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Abstract: Schizophrenia has been conceptualized as a disorder of altered brain connectivity (i.e. dysconnectivity). Until relatively recently, it was not feasible to test dysconnectivity hypotheses of schizophrenia *in vivo*. Resting-state functional magnetic resonance imaging (fMRI) is a powerful tool for mapping functional networks of the brain, such as the default mode network (DMN), and investigating the systems-level pathology of neurological and psychiatric disorders. In this article, we review the latest findings from resting-state fMRI studies on schizophrenia. Despite the wide array of methods used and heterogeneity of patient samples, several tentative conclusions may be drawn from the existing literature. 1) Connectivity of the DMN is altered in schizophrenia. Findings vary across studies; however, a majority of investigations reported hyper-connectivity of the DMN. 2) Resting-state connectivity of the prefrontal cortex (PFC) is reduced in schizophrenia, particularly intra-PFC connectivity. 3) Cortical-subcortical networks, including thalamocortical, fronto-limbic, and cortico-cerebellar networks are altered in schizophrenia. 4) Preliminary findings indicate that functional connectivity within auditory/language networks and the basal ganglia is related to specific clinical symptoms, including auditory-verbal hallucinations and delusions. 5) Whole-brain network topology measures based on graph theory indicate that functional brain networks in schizophrenia are characterized by reduced small-worldness, lower degree connectivity of brain hubs, and decreased modularity. 6) Some of the alterations in functional connectivity observed in probands are present in unaffected relatives, raising the possibility that functional dysconnectivity is an endophenotype related to genetic risk for schizophrenia. Combined, these findings provide broad support for dysconnectivity theories of schizophrenia. We conclude our review with a discussion of the limitations of the existing literature and potentially important areas of future research.

Keywords: Schizophrenia, Resting-state fMRI, Dysconnectivity.

INTRODUCTION

From the earliest descriptions of the disorder to contemporary neurobiological theories, schizophrenia has often been conceptualized as a disorder of altered brain connectivity, or "dysconnectivity" [1]. Dysconnectivity theories range from early descriptions of the phenomenology of the disorder, which emphasized the dysconnect between affect, cognition, and behavior (e.g. Bleuler 1911, cited in [2], to systems-level hypotheses that posit the disorder results from disruption of large-scale brain networks [3], to molecular models focused on alterations at the level of the synapse and cortical micro-circuitry [4]. Post-mortem studies have furnished evidence of altered cortical microcircuitry in schizophrenia, while neuroimaging has revealed widespread changes in brain structure and function *in vivo*. Structural brain changes include ventricular enlargement and reduced volume of the hippocampus, thalamus, lateral temporal cortex, and prefrontal cortex [5-7]. Functional alterations include altered activity of the lateral and medial frontal cortex, thalamus, and parahippocampal gyrus [8,9]. Some of the changes in brain structure and function are observed at illness onset and may predict transition to a full-blown psychotic disorder in individuals at high-risk for psychosis [10-12]. Reconciling the wide array of structural and functional changes into parsimonious models of the disorder remains a challenge made all the more difficult by the significant gaps in our understanding of the large-scale functional architecture of the human brain.

The emergence of resting-state fMRI, which is typically employed to examine temporal coherence, or correlation, of fMRI blood-oxygenation-level-dependent (BOLD) signal fluctuations across brain regions (i.e. functional connectivity), has dramatically improved our understanding of the functional architecture of the human brain and opened new avenues of research into the systems-level pathology of schizophrenia. The most well-known resting-state network, which has become almost synonymous with resting-state fMRI, is the default mode network (DMN). The term "default mode" was originally coined to describe a collection of brain regions consisting of the medial prefrontal cortex (PFC), precuneus, lateral parietal, and temporal lobe structures that consistently demonstrated greater activity during control conditions (e.g. rest) compared to cognitively demanding tasks in task-based imaging studies [13]. Subsequent investigations found that activity in these regions was functionally coherent during rest, confirming the notion that these regions form a network [14]. There is now overwhelming evidence that the DMN is just one of several networks that demonstrate coherent activity at rest [15]. Indeed, many networks inferred from conventional task-based imaging

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demonstrate coherent activity at rest [16]. These include sensory and motor networks comprised largely of primary sensory and motor cortices, and higher-order, "cognitive" networks consisting of heteromodal association areas; namely the frontal-parietal or executive control (ECN), dorsal attention (DAN), and salience networks [17-19].

There are several properties of resting-state fMRI that make it a useful method for uncovering the neural substrates of neuropsychiatric illnesses and a potentially useful clinical tool for tracking disease progression, monitoring treatment response, and predicting outcome. The most obvious advantage of resting-state fMRI over conventional task-based imaging is the avoidance of task performance confounds. In typical task-based imaging studies, the fMRI BOLD response is compared between task and control conditions; regions demonstrating greater BOLD response during the task compared to control condition are said to be "activated" by the task. The patterns of activation are then compared between patient and control groups to identify regional changes in brain activity associated with neuropsychiatric or neurological disorders. Inferences made using this approach are valid, provided that patients perform the task as well as control subjects. If patients perform markedly worse than controls, then it's possible that patients used different cognitive processes than controls. In the most extreme case, where patients perform at chance, they may not have even been engaged in the task at all (e.g. randomly responding, suboptimal effort) and group differences in brain activity observed under these circumstances have little value in unraveling the underlying neurobiology of the disorder. Matching groups on the basis of task performance or examining correct trials only in an event-related design solves some of these issues; however, performance matching comes with its own set of interpretational issues. Matching groups on performance often results in selective recruitment of patients that, by definition, are not cognitively impaired, at least on the task under investigation. This raises serious questions about the extent to which findings from task-based studies generalize to the broader population of schizophrenia patients given that most patients demonstrate at least some degree of cognitive impairment [20]. Since there is no task, resting-state fMRI avoids this confound, thereby expanding the proportion of patients that can be imaged and improving the probability that results will generalize to the broader population of individuals with schizophrenia.

Despite the advantages of resting-state fMRI, particularly for clinical studies, the idea of examining brain function during unconstrained mental activity was initially viewed with skepticism and the validity of resting-state functional connectivity was vigorously challenged [21]. These criticisms have been quelled to a large degree by convincing evidence that networks derived from functional connectivity in BOLD signal fluctuations during rest are highly reproducible across laboratories and reasonably reliable within subjects scanned over time [22]. Critically, evidence that resting-state networks correspond to well-known anatomical and functional networks, are supported by white matter connectivity, correlate with cognitive and emotional functioning, and are related to neural activity, further supports their validity [17,23-25].

The goal of this article is to provide an up-to-date review of resting-state fMRI studies in schizophrenia, discuss the limitations of the existing literature, and present potentially fruitful avenues of future research. We begin with a brief review of resting-state fMRI methods.

RESTING-STATE fMRI: THE METHODS

Resting-state fMRI studies typically examine functional connectivity based on temporal coherence (i.e. correlation) of the BOLD fMRI signal across brain regions. Since many non-neuronal factors contribute to the fMRI BOLD signal, including head motion and physiological artifacts (e.g. respiration), it is important to eliminate these signals or reduce their influence as much as possible. In terms of frequency, low frequencies (<.1 Hz) contribute the most to functional connectivity, whereas higher frequencies, which are associated with cardiac and respiratory signals, contribute relatively little [26]. Consequently, band-pass filtering is typically employed to remove higher (>0.1 Hz) frequencies associated with physiological noise and very low frequencies (<.01 Hz) related to signal drift. Spurious contributions to the BOLD signal related to head motion, white matter, and CSF are also removed. Another popular, but somewhat controversial step, entails removing the global, or whole-brain signal, which is simply the average BOLD signal derived from all voxels in the brain or grey matter. This step is useful as it further reduces the contribution of physiological noise to the BOLD signal and markedly improves spatial specificity of resting-state networks [27]. However, one consequence of removing the global signal is the introduction of negative correlations, or anti-correlations, between brain regions [28]. For example, following global signal removal, key components of the DMN demonstrate strong anti-correlations with regions comprising the dorsal attention and executive control networks, which were original referred to as the "task positive" network [28]. A comprehensive discussion of anti-correlations in resting-state fMRI data is beyond the scope of this review. However, we raise the issue herein to alert the reader to the unresolved controversy regarding the interpretation of anti-correlations in resting-state functional connectivity data.

Following pre-processing, there are two general classes of methods used to measure functional connectivity: 1) seed-based, region-of-interest (ROI) approaches; and 2) independent component analysis (ICA). Typical seed-based methods entail extracting the BOLD time-course signal from an a-priori defined ROI (i.e. seed), or set of ROIs, and correlating the seed time course with the time courses of every voxel in the brain. This method results in the creation of statistical maps showing the strength of connectivity (i.e. correlation) between the seed and every voxel in the brain. We refer to this approach as the "seed-to-voxel" method throughout the remainder of the article. ICA on the other hand is a multivariate, model-free, data driven method that, when applied to fMRI data, extracts the underlying temporal and spatial configuration of independent components within the time-series data (see [29] for review of ICA methods). In contrast to seed-based approaches, ICA does not require ROIs to be specified in advance. Rather, ICA is used to identify the components within the entire dataset (i.e. voxel-wise fMRI time course data) that are maximally independent.

In general, the two methods yield comparable results and major networks of the brain are detected with both approaches [30]. However, there are important conceptual differences between the two methods that need to be considered in order to better understand when they should be used and the differences in the results they yield. Seed-based methods are well-suited for testing hypotheses about connectivity of specific brain regions or connectivity between a set of predefined areas. The post-hoc nature of ICA, at least as it is typically applied to fMRI data, is ill-suited to testing a-priori hypotheses about connectivity of a pre-defined structure, or between a-priori defined brain regions, because the number and spatial configuration of components is not known ahead of time. On the other hand, ICA is generally better suited than seed-based methods at examining multiple networks simultaneously and for generating novel hypotheses that can be subsequently tested using a-priori approaches.

In addition to the seed-based and ICA methods, a third approach which looks at topological properties of brain networks, can also be described. Global connectivity approaches are conceptually similar to seed-based methods in that pre-defined ROIs are used. However, in contrast to standard seed-based methods that quantify connectivity between a single ROI, or small number of ROIs, and the rest of the brain on a voxel-wise basis, global connectivity approaches typically look at connectivity amongst a large set (e.g. 100+) of pre-defined brain regions. Typically, this is accomplished by parceling the brain into a set of regions, or nodes, and calculating the correlation matrix amongst these regions. Network measures based on graph theory can then be calculated on the correlation matrix. Key network measures include overall network efficiency (i.e. "small-worldness"), degree connectivity (i.e. the overall connectivity of a brain region), and modularity, or community structure of the brain (see [31] for a review of commonly used graph theory metrics). Relatively few studies have applied these methods to resting-state functional connectivity data in schizophrenia; however, the popularity of graph theory approaches to analyzing fMRI data is increasing rapidly.

NEURAL BASIS OF RESTING-STATE fMRI NETWORKS

The validity of functional connectivity measured during resting state hinges upon the assumption that spontaneous fluctuations in low frequency BOLD signal have a neural origin. Evidence that functional connectivity is dependent on the integrity of white matter tracts indirectly supports a neural origin of resting-state networks. Resection of the corpus callosum for example, as is sometimes done for the treatment of intractable seizures, completely abolishes interhemispheric functional connectivity [23]. Combined DTI and resting-state investigations in healthy subjects have found that functional networks are supported by white matter connections and the magnitude of functional connectivity between any two brain regions correlates with the strength of white matter connectivity [24,32,33]. However, brain regions not sharing a direct structural connection can still demonstrate robust functionally connectivity, suggesting that resting-state functional connectivity reflects both mono- and poly-synaptic influences [32].

Studies combining direct measurement of brain activity with resting-state fMRI provide the strongest support for a neural basis for resting-state functional connectivity. In humans, patients with epilepsy who have undergone electrode implantation provide a unique opportunity to investigate the neural basis of resting-state functional connectivity. One such investigation found that the spatial distribution and magnitude of temporally correlated low-frequency BOLD signals during rest predicted the pattern and amplitude of evoked responses to single-pulse electrical stimulation of the cortex [25]. In terms of frequency, both gamma band oscillations and slow cortical potentials demonstrate similar correlation patterns as spontaneous BOLD signal fluctuations measured during resting-state [34,35]. Invasive electrocorticography has revealed that gamma band-limited power fluctuations in the .01-.10 Hz range maintain coherence over relatively large spatial distances (>1 cm), whereas raw local field potentials and band-limited power fluctuations in other bands do not [36]. Combined, these findings indicate that functional resting-state networks are supported, in part, by white matter connectivity, correspond closely to evoked patterns of electrical brain activity, and are related to gamma band power fluctuations and slow cortical potentials.

RESTING-STATE FUNCTIONAL CONNECTIVITY DISTURBANCES IN SCHIZOPHRENIA

Default Mode Network Abnormalities in Schizophrenia

Resting-state functional connectivity of the DMN has been extensively studied in schizophrenia using both seed-based and ICA approaches. An overview of the findings is presented in (Table **1**). With few exceptions [37], most studies found altered resting-state functional connectivity of the DMN in schizophrenia. However, results are variable and include reports of hypo-connectivity, hyper-connectivity, and increased connectivity between DMN and non-DMN brain regions. The first investigation of resting-state functional connectivity used the seed-based approach to examine functional connectivity of the posterior cingulate cortex (PCC), a key node of the default mode network [38]. Bluhm and colleagues found that PCC connectivity with lateral parietal, medial PFC, precuneus, and cerebellum was reduced in schizophrenia [38]. Reduced DMN functional connectivity, particularly within the posterior cingulate and medial PFC hubs of the network, was subsequently replicated and linked to cognitive impairment [39,40].

In contrast to the handful of studies reporting reduced DMN connectivity, several investigations found increased functional connectivity within the DMN or reduced anti-correlations between the DMN and non-DMN brain regions [41-49]. For example, Whitfield-Gabrieli and colleagues reported increased DMN connectivity within the medial PFC and PCC, and reduced anti-correlation between the medial PFC and dorsolateral PFC in schizophrenia during resting state blocks of a working memory task [43]. Hyperconnectivity of the DMN was subsequently replicated by several groups [41,42,47,48,50]. Interestingly, the spatial topography of the DMN appears to be enlarged in schizophrenia. Specifically, both seed-based and ICA approaches found that the DMN is expanded in schizophrenia to include regions of the lateral PFC, orbital PFC, and lateral temporal lobe not normally considered part of the DMN, or only weakly connected to it [42,48,50].

Table 1. Review of Resting-state fMRI Studies of the Default Mode Network in Schizophrenia

Study	Sample Size (NC/SZ)	Connectivity Method	Findings (Schizophrenia Compared to Healthy Controls)
Bluhm *et al.,* 2007 [38]	17/17 (Paranoid)	Seed-Based (PCC)	↓ PCC connectivity with medial prefrontal, lateral parietal, and cerebellum
Zhou *et al.,* 2007 [44]	18/18 (Paranoid)	Seed-Based (DMN ROIs)	↑ Correlation within DMN ROIs
Jafri et al. 2008 [45]	25/29	ICA	↑ Correlation of the DMN component with other network components
Whitfield-Gabrieli *et al.,* 2009 [43]	13/13 (Early Phase)	Seed-Based (mPFC, PCC, LP)	↑ mPFC and PCC connectivity; ↓ Anti-correlation with dlPFC
Mannell *et al.,* 2010 [48]	16/16	Seed-Based (PCC, ACC); ICA	↑ Posterior (PCC) DMN connectivity; ↓ Anterior (ACC) DMN connectivity
Skudlarski *et al.,* 2010 [46]	27/27	K-Means Clustering (28 ROIs)	↑ DMN connectivity
Salvador *et al.,* 2010 [41]	40/40 (Chronic)	Seed-Based (90 ROIs)	↑ Medial/orbital frontal connectivity with basal ganglia, insula, and prefrontal cortex
Rotarska-Jagiela *et al.,* 2010 [40]	16/16 (Paranoid)	ICA	↓ DMN connectivity in PCC and hippocampus
Ongur *et al.,* 2010 [49]	15/14	ICA	↑ DMN connectivity in prefrontal cortex and basal ganglia; ↓DMN connectivity in ACC
Woodward *et al.,* 2011 [42]	61/42	Seed-Based (PCC)	↑ PCC connectivity with prefrontal cortex and lateral temporal cortex
Chai *et al.,* 2011 [47]	15/16 (Chronic)	Seed-Based (mPFC)	↓ Anti-correlation between mPFC and dlPFC
Camchong *et al.,* 2011 [39]	29/29 (Chronic)	ICA	↓ Connectvity in mPFC and ACC
Wolf *et al.,* 2011 [37]	10/14 (Tx Refractory)	ICA	• No differences
Mingoia *et al.,* 2012 [50]	25/25	ICA	↑ Inferior frontal and temporal gyrus,frontal polar cortex; ↓Medial and superior frontal cortex

Abbreviations: ACC=Anterior Cingulate Cortex; dlPFC=Dorsolateral Prefrontal Cortex; DMN=Default Mode Network; ICA=Independent Components Analysis; LP=Lateral Parietal; mPFC=Medial Prefrontal Cortex; NC=Normal Control; PCC=Posterior Cingulate Cortex; ROI=Region-of-Interest; SZ=Schizophrenia

Drawing conclusions from the existing literature is challenging due to the marked differences in methods used across studies, small sample sizes in a number of cases, and heterogeneity of patient groups. Nonetheless, it is noteworthy that most studies found increased connectivity within the DMN and greater connectivity, or reduced anti-correlations, with brain regions not normally considered part of the DMN, such as the dorsolateral PFC and temporal lobe. Evidence of DMN enlargement and reduced segregation between the DMN and other functional brain networks may provide indirect support for neurodevelopmental theories of schizophrenia. Functional brain networks undergo significant changes during development. Specifically, during brain maturation, short range connections weaken, within network connectivity increases, and connectivity between networks decreases [51]. Consequently, expansion of the DMN to include regions adjacent to the normal topography of the DMN and increased connectivity between DMN and non-DMN brain regions suggests that the etiology of schizophrenia may disrupt the normal processes of network integration and segregation that occur during brain maturation.

Prefrontal Cortex Dysconnectivity in Schizophrenia

With few exceptions [52], reduced resting-state connectivity of the PFC, particularly the dorsolateral PFC has been consistently reported in schizophrenia [40,42,53,54]. In a resting-state study of 17 first-episode schizophrenia (FES) patients, Zhou *et al.*, (2007) found significantly reduced functional connectivity between dorsolateral PFC and the parietal lobe, PCC, thalamus and striatum. Reduced PFC connectivity was subsequently replicated by Rotarska-Jagiela [40], Woodward *et al.*, [42], and Cole *et al.* [54]. Interestingly, despite using different methods, each of these studies found that connectivity within the PFC was reduced in schizophrenia. For instance, Woodward *et al.* [42] reported reduced connectivity between a dorsolateral PFC seed and the right middle frontal gyrus in schizophrenia. The findings reported by Cole *et al.* [54] are particularly noteworthy as they employed a "global" connectivity method that examined functional connectivity within the PFC on a voxel-wise basis. Using this method, they found that the functional connectivity of the right dorsolateral PFC and left inferior frontal junction with the rest of the PFC was reduced in schizo-

phrenia. Moreover, reduced intra-PFC connectivity correlated with greater cognitive impairment [54]. Combined, the results provide strong evidence of reduced connectivity within the PFC in schizophrenia and suggest that reduced intra-PFC connectivity is related to cognitive impairment.

Thalamocortical, Cortico-cerebellar, and Fronto-limbic Functional Connectivity in Schizophrenia

Several theories of schizophrenia postulate that the disorder results from abnormal functional interactions between the cortex, sub-cortical structures, and cerebellum [3,55]. For example, the cognitive dysmetria hypotheses developed by Nancy Andreasen posits that the myriad of symptoms associated with schizophrenia are the consequence of a core defect in coordinated information processing, termed "cognitive dysmetria," which results from abnormal functional interactions between the cortex, thalamus, and cerebellum [3]. Thalamocortical networks are arranged topographically such that distinct cortical areas, including prefrontal, parietal, motor, and sensory cortices are reciprocally connected to specific thalamic nuclei [56]. For example, the prefrontal cortex is reciprocally connected with the dorsomedial nucleus, whereas sensorimotor cortical areas are connected to ventral lateral and ventral posterior-lateral regions of the thalamus, respectively [56]. Given the prolific connectivity profile of the thalamus, disruption of thalamocortical networks may explain the wide array of clinical and cognitive disturbances observed in schizophrenia [57]. Conventional task-based functional imaging and resting-state fMRI have provided broad support for thalamocortical network dysfunction in schizophrenia, including reduced prefrontal-thalamic connectivity [46,58]. However, the topographical arrangement of thalamocortical networks also suggests that some thalamocortical networks may be more affected than others; a hypothesis that would be difficult to test using task-based fMRI and typical seed-based or ICA resting-state fMRI methods.

Borrowing a method initially applied to DTI to examine thalamocortical structural connectivity [59], Zhang *et al.* [60] recently showed that resting-state connectivity can be used to delineate thalamocortical networks. By parceling the cortex into prefrontal, motor, somatosensory, temporal, and parietal occipital ROIs and using these as seeds in a functional connectivity analysis, they were able to show that activity in each cortical ROI correlated with distinct, non-overlapping regions of the thalamus that corresponding very closely to known cortico-thalamic anatomical pathways [60,61]. Recently, we used this approach to examine thalamocortical connectivity in schizophrenia [62]. We found a variable pattern of changes in patients consisting of reduced connectivity between the PFC and dorsomedial thalamus, and increased thalamic connectivity with motor and somatosensory cortical areas. Based on the developmental trajectories of thalamocortical networks, we speculated that the changes observed in schizophrenia may relate, at least in part, to abnormal late brain maturation. Specifically, PFC-thalamic connectivity is established during late adolescence/early adulthood, whereas motor and somatosensory cortical connectivity with the thalamus is maximal in adolescence compared to childhood and adulthood [63]. Therefore, the combination of decreased PFC-thalamic connectivity and increased somatomotor-thalamic connectivity observed in schizophrenia may result from an abnormality in late brain maturation that disrupts the normal development of prefrontal connectivity and refinement of somatomotor connectivity that occurs during the transition from adolescence to adulthood.

Consistent with the cognitive dysmetria model articulated by Andreasen [3], resting-state studies have also furnished evidence of altered cortico-cerebellar connectivity. Two studies, both using seed-based approaches, found widespread reductions in functional connectivity between cerebellum and cortex [64,65]. Specifically, Collin *et al.*, [64] found that cerebellar connectivity with mid cingulate, supplementary motor area (SMA), inferior frontal gyrus, thalamus, and hippocampus was reduced in a relatively large sample of schizophrenia patients. Interestingly, Liu *et al.* [65] also found reduced cerebellar connectivity with thalamus and mid cingulate in a smaller sample of 10 schizophrenia patients.

Resting-state connectivity of other sub-cortical structures has received relatively little attention. However, it is noteworthy that two separate studies, both using the seed-based approach, found that amygdala connectivity with ventral-medial PFC is reduced in schizophrenia [66,67]. Moreover, reduced amygdala connectivity with the ventral-medial PFC has been linked to both self-rated and objective measures of aggression [66]. Consequently, resting-state fMRI of fronto-limbic connectivity may prove useful for predicting aggression in schizophrenia and elucidating the neural basis of treatments/interventions designed to reduce aggression.

Clinical Symptom Correlates of Resting-state Dysconnectivity in Schizophrenia

Several investigations of resting-state connectivity in schizophrenia reported correlations between functional dysconnectivity and clinical symptoms of the disorder, including positive and negative symptoms. For example, both Whitfield-Gabrieli *et al.* [43] and Woodward *et al.* [42] found that hyperconnectivity of the DMN is associated with worse clinical symptoms. However, the post-hoc, exploratory nature of many of these analyses raises concerns about elevated Type I error rates [68]. In contrast, several studies have taken a hypothesis driven approach to investigating the relationship between functional connectivity and clinical symptoms, focusing mainly on the relationship between auditory/language networks and auditory hallucinations. Using a seed-based approach, Vercammen *et al.* (2010) examined functional connectivity among a set of regions implicated in inner speech and auditory-verbal hallucinations (AVH) in a sample of patients with medication resistant AVH. They found that functional connectivity between the left temporal-parietal junction (TPJ) and right homotope of Broca's area was reduced in patients with medication resistant AVH. Moreover, reduced connectivity between left TPJ and bilateral anterior cingulate was associated with more severe AVH. Similar results were reported by Wolf *et al.* [37] using ICA. Specifically, they found that anterior cingulate connectivity with the left fronto-parietal network, which included the TPJ, was reduced in schizophrenia, and related to the severity of AVH. Combined, these findings suggest that functional connectivity of auditory/language processing networks is altered in schizophrenia and related to the severity of AVH. The convergence of findings on the anterior

cingulate is provocative given the prominent role this region plays in cognitive control [69]. Some investigators have speculated that the loss of functional connectivity of the anterior cingulate with posterior temporal cortex may lead to disconnection between verbal thought and conscious control, and a misattribution of internally generated thoughts to an outside agency [70,71].

Recently, Sorg *et al.* [72] examined the relationship between positive symptoms of schizophrenia and resting-state functional connectivity within the basal ganglia during both acute illness exacerbation and remission stages [72]. Their investigation was prompted by the well-established link between dopamine dysregulation in the basal ganglia and positive symptoms of psychosis [73,74]. Interestingly, Sorg *et al.* (2012) found that functional coherence in the basal ganglia, particularly the putamen, is increased in schizophrenia patients experiencing an acute psychotic episode. Moreover, the severity of positive symptoms (delusions and hallucinations) during psychosis positively correlated with functional coherence in the putamen. Remarkably, functional connectivity within the striatum decreased to near normal levels at remission. It is noteworthy that a recent meta-analysis of presynaptic dopamine imaging studies in schizophrenia concluded that dopamine signaling is elevated mainly in the putamen in schizophrenia [73]. The convergence of altered resting-state functional coherence and elevated dopamine signaling in the putamen, along with evidence that dopamine alters striatal intrinsic activity suggests that the relationship between functional coherence in the putamen and psychosis may relate to elevated dopamine signaling [75,76].

Whole-brain Functional Network Topology Changes in Schizophrenia

As mentioned earlier, there is growing interest in applying the tools of network science, namely graph theory, to better understand the brain and dysconnectivity in neuropsychiatric disorders. Briefly, graph theory is an area of mathematics that deals with the properties and analysis of graphs, which are defined as a set of vertices (i.e. nodes) that are connected by edges, much like a correlation matrix (see [31] for a review of graph theory methods for neuroimaging data). In the case of functional brain networks, an N x N binary graph consists of N nodes and undirected edges between nodes, where nodes represent brain regions and edges the functional connectivity between regions. A variety of network measures can be calculated on a graph. Popular measures of brain networks include:

- *Small-world (sigma):* Networks can be conceptualized as lying on a continuum that ranges from fully regular (e.g. a ring lattice in which each node is connected to its neighbor and its neighbor's neighbor) to fully random (e.g. connections between nodes are randomly distributed). Small-world networks lie between these two extremes and are characterized by a higher proportion of densely connected nodes (i.e. highly clustered nodes) relative to path length. Small-world networks are efficient as relatively few edges must be traversed for information to flow from any given node to another.
- *Degree of connectivity:* As mentioned earlier, graphs are composed of nodes (i.e. brain regions) and edges (i.e. functional connectivity between nodes). Nodes that are connected to many other nodes have a high degree connectivity, whereas nodes that share few connections with other nodes have low degree connectivity.
- *Modularity:* Nodes may separate into distinct communities in which nodes within a community are strongly connected to one another, but sparsely connected to nodes in different communities.

Studies of brain networks using graph theory indicate that whole-brain functional connectivity in healthy subjects are small-world networks, contain hubs with high degree connectivity, such as the PCC, medial PFC, dorsolateral PFC, and supramarginal gyrus, and form modules that correspond to well described networks, including the DMN and ECN [77-79]. In contrast, functional brain networks in schizophrenia are characterized by reduced small-worldness, lower degree connectivity of key brain hubs, and decreased modularity [77,80-83]. Reduced small-worldness in schizophrenia is a result of decreased clustering and increased diversity of connections [77,80]. In effect, functional brain networks are organized more randomly in schizophrenia than healthy subjects. In addition, modularity is reduced indicating that the degree of integration within networks, and segregation between networks is reduced in schizophrenia, a finding that parallels some seed-based studies [42,81,83]. Interestingly, reduced small-worldness, decreased hub-like organization, and a greater diversity of connections results in greater robustness to attack, leading to speculation that reduced expression of schizophrenia may confer a potential benefit [80].

FUTURE DIRECTIONS OF RESTING-STATE STUDIES IN SCHIZOPHRENIA

Despite the growing popularity of resting-state fMRI in schizophrenia, there are a number of limitations and unresolved questions that remain to be addressed. We highlight four broad areas that may prove to be fruitful avenues of research.

Longitudinal Changes in Functional Connectivity

Schizophrenia is typically conceptualized as a neurodevelopmental disorder [84]. Neurodevelopmental hypotheses of schizophrenia are based on the fact that key features of the illness, such as cognitive impairment and structural brain changes, either predate the onset of florid psychotic symptoms or are detectable at the time of illness onset [85,86]. Consequently, network changes observed in schizophrenia are often interpreted from a developmental perspective [42,62]. However, several recent longitudinal imaging studies have found evidence of progressive brain changes in schizophrenia. For instance, a longitudinal 18-year follow-up investigation revealed progressive loss of total cerebral, frontal, and thalamic volumes after the initial onset of schizophrenia [87]. Accelerated volume loss is particularly evident during the early stages of the illness; but has also been observed in chronic patients [88]. Given evidence of progressive changes in brain structure, it is reasonable to speculate that functional brain networks may also change over the course of the illness, as is observed in neurodegenerative disorders such as Alzheimer's disease (AD) [89]. To date, no

study has examined resting-state functional connectivity over the course of the illness, using either longitudinal or cross-sectional study designs. Such studies will be required to confirm or refute neurodevelopmental hypotheses of functional network changes in schizophrenia. In a similar vein, medication effects also remain largely unexplored. A small, uncontrolled, longitudinal study in drug naïve first episode patients found that short-term treatment with risperidone altered functional connectivity [90]. Clearly, more work needs to be done on elucidating the effect of antipsychotics on resting-state functional networks.

Data Sharing

Ultimately, it is hoped that characterizing functional dysconnectivity in schizophrenia will lead to the identification of biomarkers linked to behavioral/clinical phenotypes, etiology, treatment, and prognosis. The realization of this promise will require large sample sizes comprised of phenotypically well-characterized patients. As can be seen in Table 1, most resting-state fMRI studies in schizophrenia included relatively few patients; which may explain some of the inconsistent findings. The problem of small sample sizes is particularly problematic when studying heterogeneous disorders, such as schizophrenia, and will undoubtedly stymie efforts to identify the phenotypic and genetic correlates of functional dysconnectivity. Data sharing approaches will help overcome some of these barriers. There are many challenges to sharing and integrating functional imaging data; however, the relatively standard manner in which resting-state fMRI data are collected and analyzed, compared to task-based imaging, bodes well for data sharing initiatives [91]. The 1000 Functional Connectomes Project (FCP) dataset, which includes resting-state fMRI data on over 1400 healthy subjects scanned at 35 different sites, provides an excellent example of the feasibility and power of data sharing. In addition to demonstrating the exceptional stability and reproducibility of the functional architecture of the human brain, analyses using the 1000 FCP revealed sex and age effects on functional connectivity [30]. The ADHD-200 was recently initiated to establish a large repository of resting-state data collected in over 200 individuals with ADHD and 400 typically developing children. Similar data sharing efforts will likely accelerate the discovery of potentially important and clinically meaningful brain-behavior relationships in schizophrenia.

The need for data sharing and the creation of large datasets is perhaps most relevant to genetic studies. Resting-state connectivity within at least one network, the DMN, is heritable [92]. The heritability of other networks and measures of whole-brain network topology, such as small-worldness, has yet to be established. However, some of the functional connectivity changes observed in patients are present in their unaffected relatives implying a genetic contribution to network dysfunction in schizophrenia. For example, similar to probands, dysconnectivity of the DMN and cortico-cerebellar networks has been detected in unaffected relatives of patients [43,64,93]. Findings from a recent investigation indicate that inter-network dysconnectivity observed in patients, particular between the fronto-parietal network and other networks, is also present in unaffected siblings [94].

With respect to molecular genetics, the genome-wide association study (GWAS) identified risk allele rs1344706 polymorphism of the zinc finger protein 804A (ZNF804A) gene has been linked to reduced prefrontal inter-hemispheric connectivity, an abnormality consistently observed in patients [95-97]. Interestingly, the relationship between rs1344706 polymorphism of the ZNF804A gene and prefrontal-inter-hemispheric connectivity persists across resting-state, working memory, and emotion processing conditions, suggesting that the genetic effect transcends cognitive state [97]. However, the association between ZNF804A genotype and reduced dorsolateral PFC connectivity with the hippocampus is only observed during working memory. This finding illustrates the potential for resting-state fMRI to investigate genetic influences on the large-scale functional organization of the brain, but also highlights the importance of adequately characterizing connectivity disturbances across cognitive states.

Resting-State fMRI as a Tool for Personalized Medicine

There are striking individual differences in treatment response and long term outcome in schizophrenia. Broadly speaking, a small minority of patients, approximately 20%, achieve complete recovery following an initial diagnosis of schizophrenia [98]. However, the majority of patients follow an episodic course characterized by acute psychotic episodes interleaved with periods of minimal symptoms and partial recovery to premorbid levels of psychosocial functioning, with a minority, perhaps 15-20%, considered treatment resistant and having very poor psychosocial outcomes [99]. It was hoped that the introduction and widespread use of neuroimaging, especially functional imaging, would lead to the identification of biomarkers that could aid in diagnosis and help predict treatment response and outcome [100]. This promise remains largely unmet. However, there are reasons to hope that resting-state fMRI may eventually prove to be a clinically useful tool. As mentioned earlier, the relative ease with which resting-state data can be collected and the greater proportion of patients that resting-state can be acquired on, compared to conventional task-based imaging, bodes well for its potential utility as a clinical tool. Studies examining the usefulness of resting-state fMRI for predicting treatment response in schizophrenia have yet to be performed. However, a recent investigation of the relationship between resting-state functional connectivity and the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in depression provides a useful demonstration of the potential for resting-state fMRI as a tool for personalized medicine. Specifically, Fox *et al.* [101] found that the efficacy of different dorsolateral PFC rTMS targets used in clinical trials was related to the degree of connectivity between each site and the subgenual cortex in healthy subjects; more effective targets were more strongly anti-correlated with the subgenual cortex than less effective targets. Moreover, dorsolateral PFC-subgenual connectivity strengths from different rTMS targets derived from healthy controls predicted treatment response in individual patient data obtained from clinical trials. Although preliminary, this finding suggests that resting-state fMRI might be used to predict maximally effective rTMS targets in individual subjects. Similar approaches may

prove useful for predicting treatment response in schizophrenia.

Resting-State fMRI as a Tool for Translational Neuroscience

Resting-state functional connectivity is conserved across species and many of the networks detected in humans, including both basic sensory/motor and higher order "cognitive" networks such as the DMN, are also present in non-human primates and rodents [102]. The fact that resting-state functional connectivity is present in animals creates novel opportunities to examine the effects of pharmacological, genetic, and developmental disruptions on the large-scale functional organization of the brain in animal models of neuropsychiatric disorders. These effects can then be compared to patients to validate existing animal models and/or guide the development of new models. A recent functional connectivity study of the APP/PS1 mouse model of AD is a good example of the potential utility of translational resting-state functional connectivity [103]. AD is associated with a marked loss of functional connectivity within the DMN and beta-amyloid deposition, a key neuropathological feature of AD, is associated with reduced DMN connectivity [79,89,104,105]. Recently, Bero *et al.* [103] found that beta-amyloid deposition in APP/PS1 mice correlated with the degree of age-related reduction in bilateral functional connectivity. Moreover, the magnitude of functional connectivity in young APP/PS1 mice predicted age related changes in bilateral functional connectivity. In the case of schizophrenia, pathophysiological models of the disorder include alterations in neurotransmitter function, genetic vulnerability, and developmental disruption [106]. Resting-state functional imaging has not been applied to animal models of schizophrenia. However, resting-state functional connectivity may prove useful for elucidating the impact of pharmacological, genetic, and developmental disruptions on the functional organization of the brain and validating animal models of the disorder. Resting-state fMRI in animal models may also prove to be a useful screen for evaluating novel pharmacological treatments.

CONCLUSIONS

Resting-state fMRI is a powerful tool for examining the functional architecture of the brain and investigating the systems-level pathophysiology of neurological and neuropsychiatric disorders. Resting-state functional connectivity is altered in schizophrenia. Despite the diversity of methods and heterogeneity of patients, several consistent findings have emerged from the existing literature. There is strong evidence that the DMN is abnormal in schizophrenia, with most investigations finding hyperconnectivity within the DMN and even expanded DMN topography. In contrast, connectivity of the PFC is reduced in schizophrenia. Additionally, connectivity of auditory processing and language networks is reduced, particularly in patients with a history of treatment refractory auditory hallucinations. With respect to cortical-subcortical connectivity, altered thalamocortical, cortico-cerebellar, and fronto-limbic connectivity has repeatedly been demonstrated in schizophrenia. Functional dysconnectivity is often interpreted within a neurodevelopmental context; however, longitudinal studies examining connectivity changes over the course of the illness have yet to be performed and the effects of antipsychotic medication on functional connectivity remain largely unknown. Family studies indicate that some of the changes in connectivity are related to genetic risk for schizophrenia and specific schizophrenia risk alleles (i.e. ZNF104A) have been linked to functional dysconnectivity. The relative ease with which resting-state fMRI data can be collected combined with the fact that connectivity is conserved across species, including rodents, makes resting-state fMRI a promising approach to investigating the systems-level pathology of schizophrenia and a potentially valuable clinical tool.

DISCLOSURES

No commercial support was received for the preparation of this manuscript and the authors have no conflicts of interest to report.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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