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Applications of Resting State Functional MRI to Neuropsychiatric Diseases

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SYNOPSIS

Resting state studies in neuropsychiatric disorders have already provided much useful information, but the field is regarded as being at a relatively preliminary stage, and subject to a number of design issues that set limits on the overall utility.

Keywords

Neuropsychiatry; resting state; default mode; functional MRI; Alzheimer; psychosis

INTRODUCTION

The presence of spontaneous, slow, fluctuating and temporally correlated activity in fMRI time series, in addition to that observed during performance of specific tasks was first mentioned in 1993 by Ogawa¹. It was realized subsequently that such resting activity, for example occurring between the motor cortices of the two hemispheres, could yield informative connectivity data². Later similar resting activity was observed in visual and auditory cortices. More recently functional connectivity was demonstrated within the brain's default mode network (DMN)³. The DMN is a group of brain regions that manifests relatively higher levels of activity in the absence of goal-directed cognition⁴. Conversely, so-called "task positive networks" (TPN's) are active during task performance. TPNs activities are anti-correlated with those of the DMN. Commonly identified TPNs include a cingulo-opercular network mediating cognitive set maintenance⁵, and a fronto-parietal network involved in behavioral initiation and guidance. Additional "intrinsic connectivity networks" (ICN's)⁶ subsume primary sensory and higher order association cortex; all are active to various degrees in states of both rest and cognitive engagement⁷. It is generally accepted that

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The Author has nothing to disclose.

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ICNs have functional relevance and are related to persisting individual differences such as temperament⁸ and intelligence⁹.

Currently, resting state functional MRI (RS fMRI) data are widely used by multiple researchers as they are relatively simple and easy to acquire, particularly in neuropsychiatrically (NP) impaired populations, as this approach requires minimal subject cooperation or alertness, is not effortful and does not necessitate cognitive engagement with a task, as summarized in Table 1. Also the default mode network (DMN) is examined most frequently in resting state studies, as it is readily identifiable, but multiple intrinsic networks are also present at rest and may be relevant depending on context. Another advantage of resting state data are that they are relatively straightforward to analyze, whether data-driven or by seed-based analysis.

At rest, brain activity fluctuates slowly at frequencies <0.1 Hz, as straightforwardly demonstrable by analysis of resting state fMRI. This activity is synchronized and coherent across brain regions in multiple reproducible circuits/networks termed variously as resting state networks (RSNs), intrinsic connectivity networks (ICNs) etc. These patterns of resting brain activity are conserved across the mammalian kingdom¹⁰ with clear analogs being evident for example even in mice. From one perspective the term “resting state” is a misnomer, because brain modules always remain active and functionally connected. RSNs manifest predictable age-related developmental and aging-related alterations¹¹, and characteristic patterns with different levels of consciousness from coma to sleep, drowsiness to rest, and are modulated in the context of cognitive task-related behaviors¹².

To expand on some of the above themes, spontaneously-occurring, temporally synchronized, spatially distributed, low-frequency signal fluctuations that reveal intrinsic connectivity networks are measured in absence of an explicit or structured task. An entire “family” of ICN’s exists, including the default mode, simple sensory-motor networks (visual, auditory, motor), and cognitively-related (executive, salience, dorsal attention) networks that “lurk” in the background in absence of a task, but become prominent with task performance even as DMN activity is usually suppressed¹³. DMN has key nodes in medial prefrontal cortex, midline posterior cingulate cortex, precuneus and mesial temporal regions including parahippocampal gyrus¹⁴. Some studies mention specifically inferior parietal lobule and anterior cingulate cortex. It is useful to pose the question of why the DMN is so persistently present. In terms of its importance, DMN is conserved across the mammalian kingdom e.g. in awake and anesthetized rats¹⁵ and monkeys^{10,16}, is present in pre-term infants^{11,17,18} and persists despite coma¹⁹ and locked-in syndrome. Network activity can be altered by manipulating the level of consciousness with anesthesia^{20,21}. It has been stated that the ‘...ability to efficiently integrate localized neuronal processing across widely distributed functionally-specialized brain regions in the service of complex cognition and behavioral control is characteristic of mature neural systems’²². Functional resting state activity is related to structural white matter connections, suggesting a generally linked structural/functional underpinning to brain connectivity²³. For example, direct comparisons between functional connectivity (FC) measured with resting state temporal correlations and white matter anatomical connectivity quantified using diffusion tensor imaging tractography show significant agreement, clearly so for the default mode network²³. This densely inter-

connected brain wiring plan is termed the “connectome”²⁴, a concept that subsumes both underlying physical/structural connections and related functional interactions²⁵. Logically, this arrangement is an efficient means to tie together diverse brain regions into circuits and to mesh them together into ordered, connected subsystems. These later can then call on a variety of similar, more distant modules in a flexible manner to serve the ever-changing needs of cognition.

On the one hand the DMN activity that emerges from this brain organization seems to be a fundamental part of normal cerebral function. On the other hand, since it is evident in rats and during coma, it may be a conceptual over-interpretation to ascribe such higher-level functions to it as planning the future and self-reflection²⁶, as is commonly done. One alternative “sentinel” hypothesis is that DMN mediates a general environmental monitoring for unexpected/salient events²⁷. Buckner²⁸ and others²⁹ hypothesize alternatively that the major function of the DMN “is to support internal mental simulations that are used adaptively”²⁸. This latter idea is attractive because many neuropsychiatric disorders are characterized by disruptions to such internal simulations. Together with the straightforwardness of collecting resting state data, this association has encouraged multiple investigators to examine DMN in multiple neurocognitive conditions.

As mentioned above, to some extent these functional patterns are dependent on hard-wired structural connections of the sort measured by DTI³⁰. Where there are measurable differences in structural connectivity, we can examine to what extent these are accompanied by resting state functional connectivity differences³⁰ and vice versa. The combination of measures may be more useful than either alone. Similarly, additional, potentially useful information is derived when resting state data are used in conjunction with task-based functional MRI assessments. Useful RS fMRI data can be acquired quickly, typically in 5 to 7 minutes, especially when using multiband sequences³¹. Pre-processing approaches of the information gathered are generally similar to those used for conventional task-based fMRI. As noted in Table 1, RS data are quickly and straightforwardly gathered³² making this approach attractive in individuals with cognitive compromise, short attention spans, claustrophobia, compromised consciousness (coma, delirium), while being relatively stable within and across scan sessions³³.

A useful recent general review of the RS field is that of Stevens²², who emphasizes that measurement of brain regional co-activation (functional connectivity; FC) is a statistical relationship showing that neural activation levels in spatially diverse brain regions are associated in the time dimension³⁴. Following pre-processing, FC can be measured using multiple analytic techniques³² (seed-based and independent component analysis are often used) and methods are generally convergent with regard to results³⁵. ICA has the attraction of identifying and potentially removing at least some head motion-induced artifacts. FC is generally assumed to represent neuronal communication across brain modules. “Effective connectivity” additionally allows claims about the causal effect that activity in one brain region has on a different region³⁶.

RS FC is never an uncontaminated measure of brain connectivity; for example MRI scanner acoustic noise, random cognition during the scan, bodily sensations, anxiety, eyes open versus closed³⁷ and other factors all modulate the resulting FC data.

After region-to-region connectivity has been assessed from the above methods, graph-theoretical (GT) methods^{38–40} provide additional information on network organization, essentially by considering all of the brain as one interconnected network. Typical indices are strength of linear correlation among nodes (defined as functionally similar brain regions) or distances between nodes. GT can also reveal how nodes are arranged topologically into subnetworks (modularity), the extent to which they belong to more local modular communities, whether they form hubs by connecting with numerous other modules as well as with other networks, and metrics of their path lengths,^{38,41–43}. GT also introduced terminology such as “small world architecture” that highlight efficiency of information transfer within/among networks⁴⁴.

Despite the many advantages of information obtained from resting state data, there need to be many cautions in collecting and interpreting this information. These are summarized in Table 2, and some will be discussed in detail below. A particular issue to pay attention to is that patients may show different DMN activity from control groups^{28,45,46,47–50} in terms of coherence, spatial extent, relative magnitude of ICNs due to diverse factors that are epiphenomena of the illness under consideration related to treatment, lifestyle, demographic, and cognitive features^{51,52}. Some of these specifics include medication, sleep^{53,54} (one reason to acquire resting state data with the subjects eyes open, is to maximize the chance that subjects are awake during data-gathering acquisition, with consequently stronger temporal BOLD signal³⁵). Physiological variables such as breathing and cardiac rate^{55,56} can affect data, – for example a shared blood supply between different brain regions may falsely suggest shared variance in resting state FC. A theoretical issue is the appropriate false positive rate control⁵⁷ to determine multiple comparison corrections. Dealing with global signal is another issue⁵⁸.

A particularly insidious confound is that of head motion in the scanner, even small degrees of which produce signal artifacts that simultaneously exaggerate calculations of connectivity estimates for nearby voxels and decrease them for distant ones^{59–61}. The bottom line is that RS connectivity estimates are typically both lower and inaccurate in neuro-psychiatric populations, and that a series of reports in these populations have had to be reconsidered^{59,62}. Going forward, issues dealt with in Table 2 need to be carefully taken into account in study design and dealt with explicitly in the resulting reports.

While clearly very important, the issue of study-related confounds may have been exaggerated by some. For example it has been argued that since “it is unimaginable that... (patients with neuropsychiatric disorders)experience the MRI environment analogously to a paid healthy volunteer.... will interfere with the so-called default pattern or with engagement of other so-called network profiles, producing a degree of ‘abnormality’”⁴⁵. I think that this argument misses the point however, since it is precisely because individuals with neuropsychiatric disorders do likely experience the scanner environment in different ways whether through paranoia, anxiety, aberrant sensory processing etc. that these

differences in and of themselves may produce characteristic illness-related patterns that differ from those of healthy volunteers, may be diagnostically useful, and thus constitute important signal rather than noise. Thus, on the one hand while it is extremely important to control for potential artifacts, especially head motion it is equally important not to throw out the baby with the bathwater. One useful validating approach with psychotic disorders, because these are heritable and familial, has been to treat neuroimaging differences from healthy controls as endophenotypes and to explore their occurrence in unaffected first-degree relatives⁶³. On the other hand a relative lack of specificity of DMN abnormalities among different neuropsychiatric disorders definitely interferes with ability to use resting state changes in the context of clinical diagnosis. To date in fact, no resting state pattern is yet practical for individual patient diagnostic use.

Although for simplicity's sake, the DMN is most frequently extracted and examined from RS data analysis of resting fMRI information reveals multiple additional circuits—ICNs—some of which are involved in key aspects of cognitive processing but nevertheless invariably present in the background at rest and therefore amenable to analysis. Resting data have been demonstrated to correlate with both task-related behavioral performance and activation in task-associated brain regions^{64,65}. Disease-related abnormalities often affect relationships within and among multiple ICNs, not just within the DMN. Independent component analysis (ICA) is one convenient means of identifying ICNs. Using ICA-derived components one can examine not only correlational relationships within distinct components (functional connectivity; FC), but also such relationships pairwise across separate components, (functional network connectivity; FNC). Some of the key questions that can be usefully posed for a particular disorder are shown in Table 3. Because this brief review is not meant to be exhaustive, and resting state data has been used to examine literally dozens of neuropsychiatric disorders, the below we will focus on several disease states that have been most commonly considered in the literature.

ALZHEIMER'S DISEASE AND ITS PRECURSOR, AMNESTIC MILD COGNITIVE IMPAIRMENT (MCI)

Typical, late-life onset AD is usually first identified and subsequently studied by cognitive symptoms, usually beginning with short-term memory deficits and gradually progressing to involve all cognitive functions and to interfere with activities of daily living. By the time that initial amnesic symptoms are apparent, the early clinical phase designated as amnesic mild cognitive impairment, the underlying pathologic process has likely existed for many years and has already crossed a critical threshold to allow symptomatic expression. In studying Alzheimer disease evolution, the ideal design is to have longitudinal studies of healthy individuals or those at increased risk. This allows for correlation of emerging early symptoms with associated brain changes. For the latter, MCI is useful but limited in that only a proportion of cases eventually evolve to the more severe state of AD. Furthermore, not all studies in the literature specify that they were studying the amnesic form of MCI that is the most relevant precursor of AD. Because the key underlying pathology of AD is known, and its anatomic distribution affects key DMN hubs as detailed below, the disorder is especially suited for resting state studies, and in some ways is the prototypical

neuropsychiatric disorder to study with this approach. Additionally AD is relatively prevalent, can be identified clinically with reasonable accuracy, and we know much about the location and progression of the putative primary pathological disease indicators, i.e. specific regional beta-amyloid and tau deposition, that can now be quantified using PET in vivo.

Krajcovicova et al⁶⁶ summarize several hundred studies of RC in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Most focus on the DMN. Although there is now much useful evidence, the field still requires need more information, especially on longitudinal relationships between RS DMN connectivity, PET amyloid measures of the presumed underlying primary pathology, PET regional glucose metabolism and clinical cognitive assessments as well as structural MRI brain biomarkers such as age and sex normed percentile hippocampal volume. A useful review exploring the relationship with AD pathogenesis is included in the paper by Simic⁶⁷. Some factors that need to be taken into account in studying this disorder are that the functional connectivity of the DMN diminishes with normal aging. Typically there is a gradual decrease in task-induced deactivation in PCC⁶⁸, partially correlated with age-related cognitive changes, but occurring within substantially intact neural circuits. This relationship survives when corrected for GMV loss⁶⁹.

The most consistent finding in mild AD and MCI is decreased DMN functional connectivity, particularly evident in PCC and precuneus and in hippocampus/parahippocampal gyrus along with DMN connectivity to other brain circuits^{70,71}. This survives correction for GM reductions⁷². These changes correlate with the severity/progression of dementia⁷³. Some reports document longitudinal alterations, for example increases in frontal cortical connectivity that may be compensatory for the underlying pathology, but that decline over time as the disease progresses.

One interesting set of relationships emerging from these investigations is that amyloid beta is deposited in DMN hub regions early in the pathogenesis of AD as documented by PET studies⁷⁴. Higher PET amyloid plaque loads correlate with reduced functional connectivity measures of parietal cortex with all other brain voxels, as assessed by RS fMRI graph theory global centrality measures⁷⁵. In the AD prodrome, amyloid plaque spatial distribution is also likely related to RS network functional connectivity⁷⁶. As the disease progresses, resting state abnormalities certainly extend beyond the default mode network⁷¹.

Why key DMN areas seem especially affected by AD may be explained by the above, and various hypotheses have sought to unearth the pathological basis for this. For example dominant early-onset types of Alzheimer's disease show very early DMN resting state changes⁷⁷, DMN regions have very high aerobic glycolysis rates⁷⁸. Also default mode cortical hubs suffer high deposition of amyloid beta in AD, suggesting that DMN neurons may be affected by activity-dependent APP processing that interacts with glutamate projection neurons^{67,79–81}. Many core DMN regions are both substantially involved in Alzheimer's disease pathologic changes and manifest reduced glucose metabolism in early AD.

Pan et al.⁸² performed a meta-analysis of 14 data sets from 12 studies that indicated that patients with amnesic MCI compared to healthy controls using a seed-based approach, showed reduced ALFF in bilateral precuneus/posterior cingulate, frontal-insular cortex, left occipital temporal cortex and right supramarginal gyrus, and increased ALFF in right lingual gyrus, left middle occipital gyrus, left hippocampus and inferior temporal gyrus. Overall MCI was associated with widespread regional changes in resting brain activity, predominantly involving the DMN, salience and visual networks. These data are generally supported by prior investigations, and by other meta-analyses of task-based studies⁸³.

There is evidence for changes in the salience and central executive networks associated with MCI and AD in addition e.g. as summarized by Joo⁸⁴. Teipel⁸⁵ summarizes studies of cortical connectivity in AD across RS fMRI, EEG rhythms and DTI-defined white matter bundles that explored interrelationships between different forms of brain connectivity. These can be revealing; for example, Patel⁸⁶ found no cognitive or white matter FA differences between 14 carriers and 22 non-carriers of ApoE4, but decreased functional connectivity in DMN regions previously implicated in AD on IC. This suggests that functional changes precede white matter structural abnormalities in these at-risk individuals.

Cortical connectivity in AD has sometimes been described as brain neural network pathology⁸⁵. For example He and others^{87,88,79} have adopted network analytic approaches to study AD, and report that the disease is associated with disruption of normal global functional organization affecting not only local connectivity but also specialized hub nodes and important long-distance connections. Other graph theory-based investigations show altered overall network topology in AD, consistent with increased randomness (greater path length and reduced clustering coefficient) fitting a model of disrupted global information integration⁸⁹. Wang et al.⁹⁰ reported reduced connectivity of the posterior DMN and executive control network in cognitively normal individuals carrying the ApoE4 allele. DMN connectivity is reported to be increased following treatment with cholinesterase inhibitor medications^{91–93}.

A review of both cross-sectional and longitudinal papers in patients with MCI and mild AD compared to controls shows general agreement that these conditions manifest a reduced correlation of RS BOLD activity across several intrinsic brain circuits including the DMN and attention-related networks. This contrasts with meta-analyses of task-based activation, where BOLD decreases occur mainly in frontoparietal and default mode networks in MCI whereas AD patients show reduced voxel activation in the visual network. Li⁸³; Sohn et al.⁹⁴ suggests that hippocampal overactivation in amnesic MCI might represent compensatory processes, while other authors have ascribed similar functions to DMN and various cognitive networks.

Key questions remaining in A.D. include elucidating the relationship between FC differences and symptoms cross-sectionally in amnesic MCI. Preliminary evidence suggests that FC in the DM and especially its posterior anatomy is disrupted in association with memory impairment in MCI and AD⁹⁵. It is unclear to what extent can resting state fMRI patterns be used to correctly diagnose MCI/AD, and what is the most useful adjunctive diagnostic information from other imaging modalities or other biomarkers such as CSF

measures. Clarification is also needed in terms of useful RS data is in predicting future clinical course, either from MCI to AD, or cognitive deterioration in the disorder at any stage. These questions are addressed in various reviews by Koch⁹⁶, Dai⁹⁷ and Zhang⁷³. DMN disconnection might predict conversion from amnesic MCI for example⁹⁸ or show utility as an imaging marker to monitor progression⁹⁹. The role of DMN changes in early AD/MCI needs to be further clarified in terms of how primary this is as a pathologic event.

The consistency between the known neuropathology of amnesic MCI/AD, regarding its distribution and evolution with disease progression and corresponding the resting brain activity changes provide some confidence for the use of resting state activity and other conditions where the neuropathology or underlying disease neurobiology are less clear.

PARKINSON'S DISEASE

This disorder is characterized clinically by symptoms related to nigro-striatal motor system dysregulation, including motor slowing, difficulties in initiating movement, a characteristic tremor and muscular rigidity. As in AD, much of the underlying pathology of PD is known, consisting here of dopamine neuronal loss in the substantia nigra pars compacta. Also analogously to AD by the time clinical symptoms are manifest there has already been significant neuronal diminution.

Several studies have examined PD using RS fMRI¹⁰⁰, plus see reviews of Tahmasian¹⁰¹; Muller-Oehring¹⁰². In PD patients with significant tremor, movement artifact is an obvious problem. Striatal neurons normally directly influence activity in DMN¹⁰³, and FC decreases plus other abnormalities in that network have been documented in PD^{104,105}. Because accessory symptoms, such as cognitive disturbances including dementia or visual hallucinations can occur in some, but not all PD patients it is important to note which studies have carefully classified PD patients by the presence or absence of such symptoms, as their presence may be associated with additional RS abnormalities. Several investigations specifically looked for resting state alterations associated with symptoms such as specific cognitive disturbance¹⁰⁶, dementia¹⁰⁷, and visual hallucinations^{108,109}. One interesting observation is that FC between the DMN and the central executive network appears to be disrupted in PD¹⁰⁴, perhaps in association with the above-mentioned cognitive symptoms. Under normal circumstances, activity in the substantia nigra and central executive network circuits are significantly positively correlated, perhaps to facilitate DMN suppression during executive circuit activation. This positive connectivity is significantly diminished in PD¹⁰⁴, in a manner that correlates with clinical severity. Other studies have looked carefully at treatment effects^{101,110} using resting state approaches. A small-scale longitudinal treatment study reported that DMN alterations were correlated with levodopa-induced clinical improvements, but that was during the course of a provocative task (face recognition)¹¹¹. A larger scale study with an RS design would be interesting to confirm and extend the original observation. The above studies highlight the importance of careful clinical descriptions of patients with a rather varied symptomatic profile, and controlling both for symptom status as well as for possible treatment confounds. Since both longitudinal evolution of symptomatology in PD, and treatment response vary considerably, the use of RS studies

early in the course of disease, in terms of documenting utility as a biological marker would be relevant to explore.

COMA

DMN activity diminishes as subjects are compared across normal consciousness, minimally conscious, vegetative state, to brain death^{112,113}. DMN appears normal in cognitively normal individuals with locked-in-state¹⁹.

PSYCHOTIC ILLNESSES INCLUDING PSYCHOTIC BIPOLAR DISORDER

Compared to better-characterized pathological conditions such as PD and AD, psychosis is clearly a collection of brain-based disorders although the underlying pathophysiology remains unclear. However a leading hypothesis is that psychosis is related to a disconnection of cortical circuits that becomes particularly prominent in late adolescence and early adult life¹¹⁴. Due to the widespread and numerous neurophysiologic abnormalities associated with schizophrenia and other psychotic disorders that likely involve apparent communication among numerous brain networks, independent component analysis-based approaches are often favored since they allow straightforward interrogation of data both within-and between such networks. Although the first report of disrupted DMN activity in schizophrenia was derived from a task-based study¹¹⁵, reports of similar abnormalities derived from RS studies followed shortly thereafter, confirming the association with positive psychotic symptoms such as hallucinations¹¹⁶. Multiple publications have appeared subsequently, with some exploring the specificity of findings to schizophrenia as opposed to schizo-affective disorder and psychotic bipolar disorder from the BSNIP consortium. As reviewed by Narr and Lever¹¹⁷, connectomic studies of schizophrenia generally agree in showing distributed network alterations, particularly those using computational analyses separating the brain into functional nodes, and offering support for the disconnection hypothesis of psychosis.

Because psychotic illnesses typically begin during late adolescence and immediately thereafter, there is an intersection between resting state FC MRI research and the study of normal adolescent development, with studies that track emerging psychosis in high-risk populations. A review of studies examining the onset of psychosis during the transition from the precursor prodromal state in schizophrenia is accompanied not only by progressive gray matter abnormalities, but also the emergence of anomalous functional connectivity patterns similar to those seen in more chronically ill individuals with the disorder¹¹⁸. The same authors review abnormal functional connectivity in a prefrontal-thalamic network among clinical high-risk for psychosis individuals in the North American Prodromal Longitudinal Study (NAPLS); subjects with the most pronounced abnormalities were most likely to show subsequent conversion to psychosis. The utility of such functional changes in predicting converting to psychosis for individuals has yet to be established.

Satterthwaite and Baker¹¹⁴ make the important point that emergence of the typical late adolescent developmental trend toward segregation of large-scale brain association networks from the usual prior less organized state fails to occur in individuals developing psychotic illnesses, placing the disconnection hypothesis in a developmental context.

Novel analyses: some recent advances in analyzing resting state activity in psychosis include dynamic connectivity approaches^{119,120} group information guided independent component analysis¹²¹, inclusion of low-frequency fluctuation measures such as ALFF/fALFF¹²². Sometimes these are coupled with machine learning approaches¹²¹. To provide examples of the above, one recent refinement on RS analyses is the use of a “chronnectome” measures to better characterize activity variation in the time domain. Rather than averaging resting state activity across the entire scan acquisition period, such dynamic connectivity approaches examine time-varying dynamic activity, using for example sliding time window methods. Such analyses can identify discrete functional connectivity states, the connectivity strength within each state, the amount of time (dwell time) spent within each state and the transition times between them. Using such an approach Du¹²⁰, was able to demonstrate that schizophrenia patients spent more time in the states with nodes sparsely connected and exhibited weaker connectivity strength within each state, lower average values for node strength, clustering coefficient, global and local efficiency than did healthy controls. These findings are consistent with impaired connectivity among DMN subsystems, with a reduction in the usual prominence for posterior cingulate and anterior medial PFC hubs. An earlier report from the same group¹¹⁹ compared both schizophrenia and bipolar patients the healthy controls. Both static (average) and dynamic connectivity were examined. Patients made fewer transitions to some dynamic states compared to controls and differences between the two clinical groups were more apparent using the dynamic approach, underlining its utility.

Use of resting state measures potentially problematic in that affected by concomitant prescribed medication as well as other factors that can impact resting state measures that are disease related confounds. Examples are that patients with psychotic disorders are more likely to have concomitant substance abuse problems, sleep disruption, be less likely to be able to stay still in scanner, which can have artifactual effects on RS measures. On the other hand DMN studies are useful in that they require little effort from subjects and do not encounter some of the problems of cognitive-based paradigms as outlined elsewhere³² that are particularly applicable to this subject population.

One consistent result from the multi-site Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP-1) study is that contrary to expectation, biological markers including resting state fMRI data are much more similar across the presumed diagnostically distinct syndromes of schizophrenia, psychotic bipolar disorder and schizoaffective disorder⁶³. Many syndromes in psychiatry are diagnosed currently on the basis of cross-sectional symptoms and longitudinal outcome, but are not defined by biological criteria. It was hoped that biological measures such as RS FC would constitute “biomarkers” for these disorders, thus validating diagnostic distinctions as reflected for example in the American Psychiatric Association’s Diagnostic and Statistical Manual. Somewhat unexpectedly however, a series of such measures including functional MRI analyses show many similarities across the three syndromes, in addition to a number of syndrome-specific alterations for example, see^{123,63}. Meda¹²⁴ compared schizophrenia and psychotic bipolar probands and their unaffected relatives to healthy controls using ICA to probe spatial aspects of functional network connectivity (FNC) in resting state networks. He detected three different network pairs that were differentially connected in schizophrenia and psychotic bipolar illness; a. frontal-

occipital, b. anterior DMN/prefrontal, c. meso/paralimbic, d. frontal-temporal/paralimbic and e. sensorimotor. The c–e pair was uniquely abnormal in schizophrenia, the c–d pair uniquely abnormal in psychotic bipolar disorder whereas the a–b combination was abnormal in both disorders. The paralimbic circuit found in networks c and d, and which uniquely distinguished bipolar probands, contains multiple regions previously identified in mood disorders of several types.

Analyzing the same data set using an ICA-based functional connectivity (FC) approach Khadka¹²⁵, documented abnormalities in five network components, two of which were unique to schizophrenia (posterior DMN and frontal-occipital) another two that were similarly abnormal in both schizophrenia and bipolar disorder (frontal-temporal/paralimbic, and midbrain/cerebellum) as well as three networks (frontal-occipital, frontal/thalamic/basal ganglia and sensorimotor) that were shared by both probands and their relatives. Additionally, several of these network abnormalities were related to current symptoms in the patient groups. Lui¹²⁶, compared to similar diagnostic sample that measured amplitude of low-frequency fluctuations (ALFF), comparing regional measures across groups. Schizophrenia and psychotic bipolar disorder probands had reduced activity in orbitofrontal cortex and cingulate gyrus compared to controls, as well as abnormal connectivity within striatal-thalamo-cortical networks. Such abnormalities were greater in schizophrenia where probands showed more severe and widespread alterations particularly in thalamus and bilateral parahippocampal gyri. The latter difference was related both to positive symptoms in cognitive deficits psychotic bipolar probands had uniquely increased FC between thalamus and bilateral insula.

A separate question that arises is whether psychotic and non-psychotic bipolar patients differ from each other, and in comparison to patients with schizophrenia and healthy controls. This question was addressed in an analysis by Anticevic¹²⁷ that examined connectivity in the ventral anterior cingulate cortex, which has been linked to regulation of emotional behavior. This functional connectivity analysis used a ventral anterior cingulate seed to reveal altered connectivity along the dorsomedial prefrontal surface. Both schizophrenia and psychotic bipolar patients showed regional connectivity reductions, in contradistinction to those bipolars without a psychotic history who showed increased coupling, compared to healthy controls. Schizophrenia patients and psychotic bipolar subjects were not significantly different from each other, again supporting the idea of commonalities among psychotic illnesses.

A useful review of by Sheffield and Barch¹²⁸, concluded that patients with schizophrenia show functional connectivity abnormalities in the resting state within and between regions comprising the cortical-cerebellar-striatal-thalamic and task-positive and task-negative cortical networks. Furthermore, these functional connectivity abnormalities were shared across cognitive domains rather than being uniquely related to any particular type of cognitive impairment. A strong theme that emerged was that the normally strongly anti-correlated task-positive and task-negative functional networks were abnormally connected in schizophrenia, in association with the wide-ranging cognitive deficits frequently seen in schizophrenia patients.

Finally a paper by Meda¹²⁹, proceeding from the fact that DMN activity is highly heritable, used parallel independent component analysis to reveal underlying genetic associations of the RS DMN in psychotic bipolar disorder and schizophrenia. The analysis identified five sub-networks each of which was significantly associated with five different SNP networks. Analysis of the implicated groups of genes uncovered several highly-ranked that had been previously implicated in psychosis and mood disorder risk. Global enrichment analysis highlighted processes that included NMDA-related long-term potentiation, immune response signaling, axon guidance and synaptogenesis that significantly influence DMN modulation in these psychotic illnesses.

Because white matter connectivity as revealed by DTI and resting state functional connectivity are clearly related²³, combining these two measures of brain connectivity provides a more comprehensive descriptions of altered brain connections associated with. One such analysis revealed a complex picture in schizophrenia, where anatomical connectivity was uniformly decreased, and where functional connectivity was lower in the middle temporal gyrus but increased in cingulate and thalamus. Overall, the picture was one of decoupling between structural and functional connectivity localized to networks originating in PCC and the task - positive network and one DMN component³⁰.

ACUTE DRUG INTOXICATION

Are there characteristic identifying patterns of different drugs or drug classes with regard to functional connectivity following acute drug challenges? This type of research is still at an early stage with regard to robust replication, but preliminary indications are that there may be differences in response patterns following acute challenge between drugs as diverse as THC¹³⁰, ketamine¹³¹, caffeine^{132,133}, morphine and alcohol¹³⁴ and nicotine¹³⁵. The latter drug increases connectivity within limbic circuits¹³⁶.

Acute drug challenge studies are particularly liable to artifacts of changes in regional cerebral bloodflow (therefore arterial spin labeling is often a useful adjunct), to changes in restlessness e.g. with psychomotor stimulant drugs, cardiac rate (psychostimulants, cannabis), respiratory rate e.g. opioids, or somnolence e.g. Benzodiazepines. The optimal design for such studies includes multiple sessions for each subject that are both placebo-controlled and use multiple drug doses together with biological drug level monitoring.

CHRONIC DRUG AND ALCOHOL ABUSE

Fedota and Stein¹³⁶ note that conceptually addiction “is a disease of intercommunicating brain networks” subserving interactions between such domains as reward, learning, affect and executive control, and thus a suitable candidate for assessment of RS functional connectivity, although many of the above caveats associated with acute drug administration apply here. Heroin users are reported to show reduced resting state connectivity in orbitofrontal cortex, thalamus and cuneus¹³⁷ and cocaine users have reduced bilateral prefrontal connectivity¹³⁸. Ventral and dorsal striatal connectivity differences in cocaine users were reduced after methylphenidate administration¹³⁹. Because nicotine is a widely-used legal drug it can be studied more straightforwardly than many other substances.

Chronic nicotine exposure diminishes network efficiency globally¹³⁶; Nicotine replacement in abstinent smokers improves patterns in resting state network dynamics, along with cognitive withdrawal symptoms¹⁴⁰. A very large scale study of several hundred individual smokers showed reduced connectivity in executive and default networks¹⁴¹. Using a seed-based approach, Hong¹⁴² showed a correlational relationship between increasing severity of nicotine addiction and reduced dorsal ACC/ventral striatal connectivity. In contrast, the same set of experiments indicated that acute nicotine doses increased connectivity in cingulate-cortical circuits but had no effect on the above dorsal ACC/ventral striatal relationship. As pointed out by Fedota and Stein¹³⁶, this may relate to low efficacy of nicotine replacement therapy in many smokers.

In conclusion, RS studies in neuropsychiatric disorders have already provided much useful information, but the field is regarded as being at a relatively preliminary stage, and subject to a number of design issues that set limits on the overall utility.

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KEY POINTS

- Numerous brain networks (e.g. default mode network) normally communicate with each other constantly, and these functional communication patterns are often disrupted in association with numerous neuropsychiatric disorders.
- Resting state functional MRI is a quick, non-invasive and convenient approach to explore these functional brain abnormalities in a quantitative manner.

The resulting patterns of disruption are useful in a research context, but do not constitute unique “fingerprints” of diseases and are not yet practical for use in making diagnoses in individual patients.

- Care must be taken in gathering and analyzing resting state fMRI data; there are numerous potential caveats and confounds, including head movement and other disease-associated but irrelevant sources of noise, that can interfere with interpretation of results.

Table 1

Utility of resting state functional MRI studies in neuropsychiatric illness.

Advantage	Corresponding Disadvantage
Acquisition simple, quick, convenient	
Replicable brain BOLD patterns	Less replicable outside of core circuitry
Requires no cognitive effort on part of patient	Lack of cognitive referent – unable to “interrogate” brain, therefore unstandardized
Allows study of infants/children, drowsy/comatose, cognitively impaired hallucinated and elderly individuals	
Analysis relatively straightforward	
Design simple enough to allow comparison across different studies	
Sensitive method	Equally sensitive to multiple confounds, as listed in Table 2

Table 2

Problems and pitfalls of resting state functional MRI studies in neuropsychiatric (NP) patients.

Problem	Result	Suggested Solutions
Neuropsychiatric (NP) patients more likely to move during image acquisition	Movement misinterpreted as actual activation	ICA to remove artifact image series, scrubbing
NP Patients more likely to use substances including recreational drugs, caffeine nicotine	Confounding change in RS activity	Screen for substances control access to nicotine & caffeine
Disease-associated confounds: altered sleep, physical activity, BMI, breathing & cardiac rates	Confounding change in RS activity	Pick analogous control group measure confound & co-vary
NP-associated elevated stress & corticosteroid levels	Confounding change in RS activity	Measure and co-vary
Severity of potentially confounding non-primary disease symptoms, e.g. dementia in Parkinson's disease, or non-primary abused substances in addictions (eg comorbid opioids in alcoholism)	Confounding changes in RS activity	Measure and co-vary. Assess comparison study group with pure secondary issue eg pure opioid users
Unstandardized acquisition conditions, e.g. eyes open vs closed, not checking if subject is asleep	Alters RS activity	Standardize acquisition conditions

BMI=body mass index.

Table 3

A general format for considering RS fMRI changes associated with neuropsychiatric disorders.

What are the disease-associated changes?
Sample size and effect sizes?
How reproducible are they, within and across subjects?
To what extent are the reported changes within (functional connectivity) and among (functional network connectivity) ICNs/RSNs associated or correlated with known structural differences on neuroimaging, neuropathology or etiologic factors where these processes are well-recognized?
To what extent are the changes cross-validated by functional abnormalities measured using different technologies, for example magnetoencephalography?
How specific are they to the disorder; for example various psychotic disorders or dementias
Are the changes related to severity of typical symptoms or deficits characteristic of the disorder?
How confident can we be that reported changes are not an epiphenomenon of associated factors and behaviors that typically differ between neuropsychiatric and healthy control groups ^{16,26,27,28,29,30,31} in terms of spatial extent, relative prominence & coherence of ICNs. (See Table 2 for a list of such confounding associated factors)