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How Can Studies of Resting-state Functional Connectivity Help Us Understand Psychosis as a Disorder of Brain Development?

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Abstract

Psychosis is increasingly being understood as a neurodevelopmental “dysconnection” syndrome, in which neural connectivity – at both microscopic and macroscopic levels of brain organization – becomes disrupted during late adolescence and early adulthood. Tools to quantify normative brain development and identify individuals at risk are urgently needed to tailor appropriate strategies for prevention and intervention, and could substantially improve clinical outcomes. Resting-state functional connectivity magnetic resonance imaging (rsfc-MRI) provides a rich, functional description of the brain’s macroscopic connectivity structure. Over the past several years, rsfc-MRI has evolved to be a powerful tool for studying both normal brain development and abnormalities associated with psychosis. Several recent advances highlight intriguing and potentially significant parallels between these two lines of research. For instance, rsfc-MRI work suggests that psychosis is accompanied by loss of segregation between large-scale brain association networks, a pattern that is normal in early life but typically matures into more segregated systems by young adulthood. Coupled with data sharing across large-scale neuroimaging studies, longitudinal assessments using rsfc-MRI in patients and those at risk will be essential for improving our biological understanding of psychosis and will help inform diagnosis, prognosis, and clinical decision-making.

INTRODUCTION

Schizophrenia is a major neuropsychiatric disorder that affects approximately 1% of the population worldwide, with frequently devastating consequences. Prior to the diagnosis of schizophrenia, sub-threshold psychotic-spectrum symptoms that impact functioning are

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common. Convergent evidence from multiple sources including animal model systems, epidemiologic data of maternal infections, and human neuroimaging has led psychosis to be increasingly understood as a disorder of neurodevelopment [1]. Such a re-conceptualization has led to the hope that a better description of the neurodevelopmental origins of psychosis will allow early interventions to “bend the curve” of abnormal brain development and lead to improved patient outcomes [2].

Resting-state functional connectivity magnetic resonance imaging (rsfc-MRI) has evolved to be a powerful tool for studying both normal brain development and abnormalities associated with psychosis. Initially described in 1995 by Biswal et al., functional connectivity is defined as time-series correlations in the blood oxygen level dependent (BOLD) signal between different brain regions, which are most predominant in low frequencies [3]. Brain regions that are functionally connected to each other are often spatially distributed, and reliably delineate large-scale functional brain networks [4,5]. Functional networks defined by rsfc-MRI accord to a remarkable degree with studies of task-based fMRI activation [6].

rsfc-MRI has certain properties that make it particularly advantageous for the study of psychosis and brain development. First, the limited behavioral demands of the acquisition procedure are an advantage: both young participants and more symptomatic patients may have difficulty performing a task paradigm appropriately in task-based fMRI studies. In contrast, the “task” of rsfc-MRI is to rest quietly. Second, the simplicity of the data acquisition procedures allow it to scale easily even to very large studies. This is a major advantage for the study of psychosis in youth, where heterogeneity is likely to be substantial. Two substantial sources of heterogeneity include normal developmental processes and biologic heterogeneity within clinical phenotypes. Effective decomposition of such heterogeneity into normative “growth charts”[7] that can be used to identify abnormalities of brain development associated with psychosis requires large-scale studies. Studies that seek to relate abnormal connectivity phenotypes to genetic data similarly require very large samples. Third and finally, rsfc-MRI provides extremely rich data regarding functional brain networks, which may be a particularly informative unit of analysis for psychotic disorders, and are amenable to many complementary analytic strategies.

Here we review the existing literature regarding how rsfc-MRI has been used to understand psychosis as a disorder of brain development. We focus on key studies of normal development, studies in adults with schizophrenia, and research from youth at-risk and those with prodromal symptoms. As described below, rsfc-MRI provides valuable evidence that a failure of functional network development may be a critical feature of psychosis, and provides a uniquely flexible tool for further research.

STUDIES OF NORMAL BRAIN DEVELOPMENT

While initial rsfc-MRI studies mapped functional connectivity in adults, the promise of examining how functional brain networks evolved in youth was quickly recognized. In a classic series of studies, Fair et al. initially described how the cognitive control system evolved into adult structure through segregation of fronto-parietal (FP) and cingulo-

opercular (CO) elements [8]. In a follow-up study Fair et al., tracked increases in connectivity within the default mode network, and noted how default mode regions became more densely connected with each other but more segregated and less strongly connected with elements of the executive system [9]. Subsequent research has provided convergent evidence. Kelly et al. found evidence for more focal within-network connectivity from a range of anterior cingulate seed regions linked to diverse cognitive and social processes [10]. Using both a discovery and replication sample, Uddin et al. found similar evidence for increased connectivity within elements of the control network and the default mode network [11]. Notably, a recent ground-breaking study by Thomason et al. demonstrated that changes in inter-hemispheric connectivity consistent with network development can even be seen in developing fetuses [12]. Overall, these findings from studies of specific brain networks suggest that *within-network* connectivity increases with development while *between-network* connectivity diminishes (see Figure 1) [13].

This hypothesis was explicitly tested on a whole-brain basis in a study by Anderson et al., who found that connectivity gradients between large-scale functional brain networks increased with development [14]. Barber et al. found similar evidence for the development of network segregation in the form of enhanced anti-correlation between the task-positive executive system and the default mode network [15]. Importantly, the strength of this relationship was related to cognitive capability (i.e., performance on a Go/No-Go task). Finally, in a high impact paper Dosenbach et al. used the complete multivariate pattern of connectivity to predict neurodevelopment on a single-subject level using a cross-validated support vector regression [16]. Notably, the strengthening of within-network connections and weakening of between-network connections were among the most highly predictive model features. This study demonstrated for the first time that evolving functional connectivity including patterns of network segregation could be used to create a normative growth chart of brain development, and raised the possibility that deviations from this trajectory could be detected within pathological conditions such as psychosis. Next, we examine evidence from studies of adults with psychosis and youth at risk within this context.

STUDIES OF ADULTS WITH PSYCHOSIS

Since well before the introduction of rs-fcMRI, changes within dorsolateral prefrontal cortex (DLPFC) have been reported in psychosis. Convergent evidence from animal models, human post-mortem tissue, and task-based functional imaging provides an elegant multi-level explanation for how cellular and synaptic changes (e.g., in parvalbumin-containing GABAergic interneurons) may lead to computational inefficiencies in DLPFC function that in turn lead to psychosis and cognitive dysfunction [17–19]. Resting state imaging has bolstered and extended these observations, placing them into a network framework. rs-fcMRI reveals, for instance, how variation in a large-scale system that includes DLPFC may alter relationships between systems responsible for other domains of information processing, and might help to explain disparate network-level findings in schizophrenia (see Figure 2) [20–26].

Several efforts that have used rsfc-MRI to survey large-scale brain systems for evidence of dysconnectivity in psychotic disorders have come to broadly similar conclusions, albeit by

distinctive analytic approaches [21,23–26]. Among such studies, reduction in BOLD time course correlation among components of the FP control network appears to be the most reproducible finding, while changes in other association networks are also frequently observed, albeit to a lesser or less reliable extent, including within the “Saliency” or ventral attention network [21,24,25,27] and the default network [21,27]. Network-wide analyses using data-driven selection of *a priori* regions and networks of interest will likely be critical to reaching consensus across these kinds of studies.[21] Primary sensory and motor networks appear to show largely intact functional connectivity patterns, according to most reports. These studies confirm the central nature of large-scale association network disruption in psychosis, and together with the task-based fMRI literature (see Barch and Caesar; [17]) support the idea that dysfunction within control networks may be a final common pathway, or shared biological substrate, for the core construct of psychosis that subsequently leads to a heterogeneous clinical presentation via idiosyncratic disruption of other large-scale brain systems in each individual.

In addition to such studies of control networks, connectivity within the default mode network has been studied extensively in psychosis. At least initially, the default network garnered considerable attention due to (a) its purported role in processing internal stimuli and representations of the self (e.g. psychological face validity), (b) its position as an information processing “hub” for the cerebral cortical network (i.e., computational face validity), (c) its amenability to rsfc-MRI analysis and relative stability across participants, and also (d) its newcomer status as a focus of study (it was first described only in the late 1990s). Whitfield-Gabrieli and colleagues found that patients with schizophrenia had *increased* within-network default network connectivity, as compared with healthy controls, in the context of a working memory task [28]. Remarkably, they also reported default network hyperconnectivity in unaffected first-degree relatives of the patients, as well as correlation among affected individuals between psychotic symptoms and default network hyperactivity during task performance, suggesting that “a failure to suppress default mode” function might represent an endophenotype or core, heritable feature of psychotic illness. Other studies in at risk populations show similar results (see “Studies of Children and Adolescents at risk” below), raising additional interest in this phenotype,[29,30] despite the lack of consistent default network findings in chronic patients.

Several rsfc-MRI studies in psychotic individuals have also highlighted changes in the interactions between cortical and subcortical systems, including the thalamus and basal ganglia, both long believed critical in the pathophysiology of psychotic illness. Abnormal functional connectivity between frontal cortex and the thalamus were observed in two recent studies [26,31]. Significantly, both studies found evidence of a mixed pattern of dysconnectivity, with reduced connectivity between thalamus and prefrontal cortex and increased connectivity between thalamus and motor cortex.

Finally, several studies have examined global changes in brain organization and function in psychosis. Using graph theoretic measures, several reports describe a broad breakdown in cortical functional organization, evidenced by reduced local network connectivity, reduced modular structure, but greater global network robustness [22,32–35]. Potentially relevant to these widespread observations, Yang et al. found that BOLD signal in the low frequency

range (< 0.1 Hz) may also be globally elevated in schizophrenia [36]. Importantly, head motion can also lead to the appearance of reduced global modularity and increased low frequency power [37,38], making careful interpretation of global changes critical for understanding and generalization of these findings (see Limitations, below). However, recent work including that by Yang et al. has rigorously controlled for such confounds [36].

Taken together, these rs-fcMRI studies of adults with psychosis have revealed intriguing, but as yet untested, parallels between the biology of normal brain development and the emergence of psychosis. The patterns seen in patients – e.g., reduced modularity and incompletely segregated FP-CO control network – have a notable correspondence to stages of normal adolescent development, raising the intriguing possibility that psychosis may delay key developmental stages, particularly in the refinement of cortical association systems. Alternatively, psychosis may represent a developmental stage, or *sensitive period*, that was never properly closed, perhaps due to oxidative stress [39], leaving brain systems in a state of extended plasticity longer than appropriate and thus vulnerable to environmental insults outside the usual developmental window. Whether these speculations have etiologic relevance will depend on detailed longitudinal assessments in individuals at risk for psychosis and in the earliest stages of illness.

STUDIES OF CHILDREN AND ADOLESCENTS AT RISK

Only a relatively small number of studies have measured functional connectivity in young individuals at risk for psychosis or with early onset forms of the illness. Two recent studies recently extended upon the Whitfield-Gabrieli findings [28], focusing on changes in DMN hyperconnectivity in early forms of psychosis. Fryer et al. reported DMN hyperconnectivity in youth at clinical high risk for psychosis and early schizophrenia in the context of a working memory task, consistent with the idea that deficient suppression of DMN activity during task performance may be present early in the disease course [29]. Wotruba and colleagues also reported similar findings, describing a loss of anticorrelation between a task-positive (i.e., FP control like) network and the DMN in individuals experiencing prodromal symptoms [30]. Fornito and colleagues recently found that individuals with early psychosis and their unaffected relatives showed corticostriatal dysregulation, with dorsal striatal hypoconnectivity and ventral striatal hyperconnectivity with cortical targets [40]. Other connectivity abnormalities have not been found to extend into the prodromal period: for example, amygdala connectivity with orbitofrontal cortex is reduced in chronic and early psychosis patients, but was preserved in high risk patients [20].

Additional research that is nearing publication also suggests intriguing dynamics of cortical network architecture around the time of psychosis onset. In a study of 129 unmedicated patients in the early stages of a psychotic illness, Anticevic et al. found evidence of hyperconnectivity between the same prefrontal-thalamic regions that show reduced connectivity in the chronic state (Anticevic et al., unpublished). Thus, early or prodromal psychosis may be qualitatively distinct biological entities compared with chronic illness. If correct, this view suggests that cortical brain systems may compensate for an early insult, which yields a state of hyperconnectivity, by systematically reducing connectivity. These tentative hypotheses require significant additional investigation in cohorts of patients who

can be followed longitudinally over the course of illness, as they progress from an at-risk to disease state. Thus, although the available data do not yet paint a clear picture of how developmental connectivity changes relate to those seen in chronic psychotic illness, they highlight the utility with which rsfc-MRI can provide key information constraining the possible biological explanations for psychosis and its emergence in young adulthood.

LIMITATIONS

Despite its numerous advantages and the results described above, rsfc-MRI is not without limitations, including limits of interpretation and susceptibility to artifact. While the low-level task in rsfc-MRI is often an advantage, this lack of constraint also limits interpretation. Effects are usually interpreted within the context of functional networks, but without supporting data from clinical, cognitive, or behavioral data such results may be easily over-interpreted.

Over-interpretation of unconstrained rsfc-MRI results is a particular risk in cases where unmeasured individual or group differences in subject motion are present. Three studies published in close synchrony recently demonstrated that even small amounts of in-scanner subject motion systematically biases measured functional connectivity [37,41,42]. As motion is often strongly related to age and clinical status, motion artifact is a major confound for developmental and psychiatric neuroimaging.

Notably, the effects of motion are the reverse of one of the most commonly reported developmental findings, which is that with development long distance connections strengthen and short-range connections weaken. Conversely, when global signal regression is used, motion is associated with a decrease in long-range connectivity and increase in short-range connectivity. Two studies systematically reassessed developmental changes in light of this artifact, and found that motion markedly inflated previous reports of distance-dependent changes in connectivity [13,43]. However, the effect of motion artifact on patterns of brain development are heterogeneous: while motion inflates estimates of distance-dependent change in connectivity, motion in fact obscures evidence of functional network segregation [13]. When motion artifact is adequately controlled, network segregation with development is more easily observable and individual age prediction remains robust (Figures 1C and 1D). More recently, advances in MRI acquisition [44] and post-processing techniques have been shown to mitigate motion artifact substantially [38,41].

ONGOING EFFORTS AND FUTURE DIRECTIONS

Taken together, the studies reviewed above emphasize that rsfc-MRI is a valuable phenotype for which to study how psychosis may be related to abnormalities of brain development. Indeed, because of its advantages, rsfc-MRI is being applied at increasingly large scales to study the developmental and genetic origins of psychosis. In the coming months, the North American Prodromal Longitudinal Study (NAPLS) is set to release its findings from its multi-site rsfc-MRI study of youth at risk for psychosis [45]. Similarly, the Philadelphia Neurodevelopmental Cohort [46] is tracking psychosis-spectrum symptoms within a large cohort of youth (9,500 phenotyped, 1,601 imaged). In combination with other large-scale

imaging initiatives including PING, the NKI-Rockland Sample, IMAGEN, PSYSCAN, PRONIA, the Genome Superstruct Project [5], B-SNIP [47], and the UK BioBank Imaging Extension, this data will provide unprecedented ability to study the evolution of functional brain networks in health and disease. Because of the likely heterogeneity in brain phenotypes associated with mental illnesses such as psychosis, combining data across large samples will be critical and facilitated by efforts to harmonize imaging acquisition parameters and clinical phenotyping strategies (i.e., the NIH Common Data Elements initiative). Data from these studies and also large-scale meta-analytic efforts such as the ENIGMA consortium [48] will provide an opportunity for integrating genomic data in order to understand how genetic vulnerability may be associated with abnormalities in functional brain networks that lead to symptoms of psychosis. Finally, new multi-band fMRI acquisition techniques [49] increasingly allow higher-resolution examination of dynamic reconfiguration of resting-state networks over time [50], which may provide novel brain phenotypes related to the development of psychosis.

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HIGHLIGHTS

- Psychosis is increasingly understood as a disorder of neurodevelopment.
- Resting state fMRI powerfully describes brain development and psychosis.
- Here we review rsfc-MRI studies of development and psychosis.

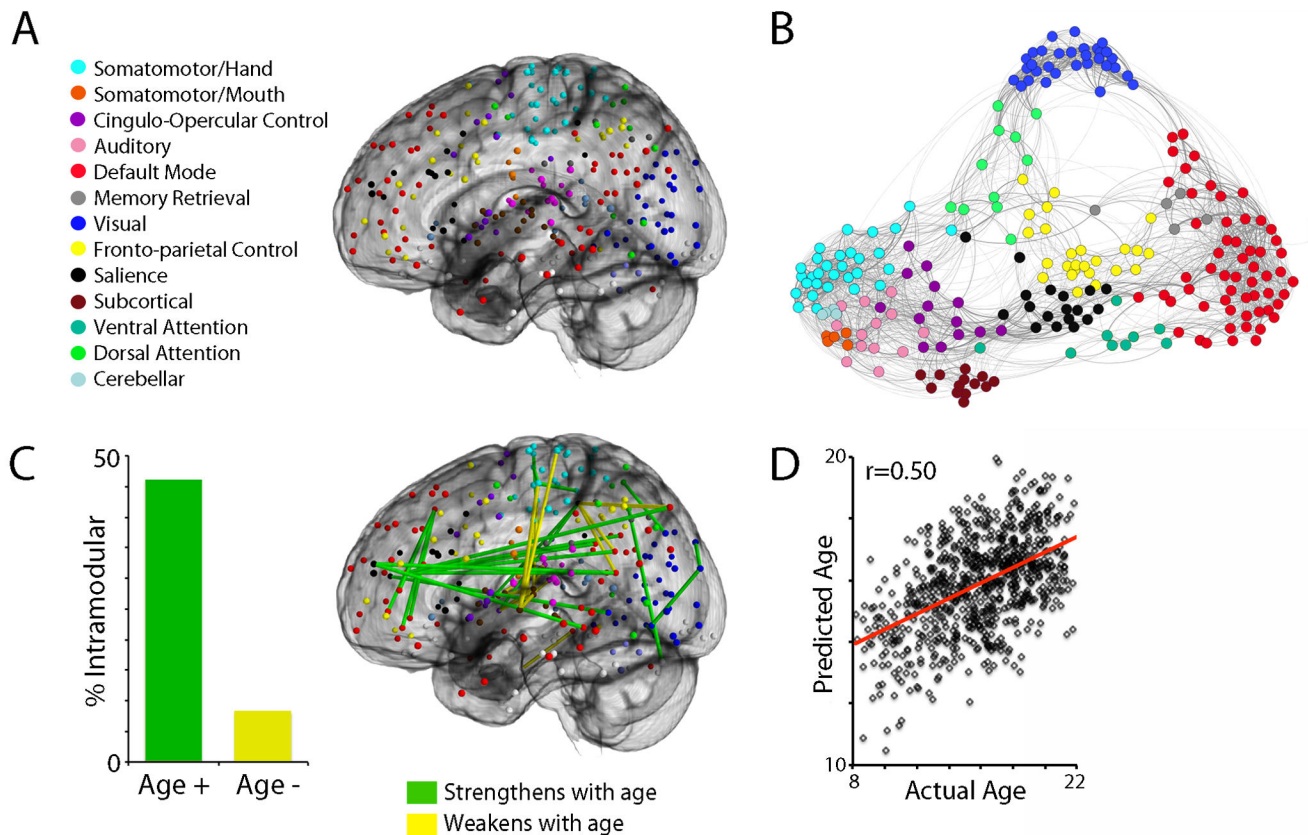


Figure 1.

(A) Functional network definition. Nodes from Power et al. (2011) define 13 large-scale functional brain networks. Nodes are colored according to module membership as indicated in the figure legend. **(B) Functional network structure.** Spring-embedded rendering of mean network connectivity matrix in a sample of 780 youth. Graph edge thickness is scaled according to connection strength. Nodes are colored by module assignment as in (A). As noted by Power et al. (2011), certain network modules (motor, visual, default) are more segregated, whereas networks implicated in cognitive control (frontoparietal, salience) display more inter-modular connections. **(C) Large-scale functional brain networks become more segregated with development.** Connections that strengthen with age are significantly more likely to be within a functional module than between functional modules. Connections that strengthen with age are displayed in green, connections that weaken with age are displayed in yellow. This effect is robust: only connections that survived that surpassed a Bonferroni-corrected statistical threshold (corrected $p < 0.05$, uncorrected $p < 1.4 \times 10^{-6}$) are displayed. Notably, this effect is enhanced when controlling for motion artifact. **(D) Multivariate patterns of connectivity accurately predict an individual's chronologic age.** Using a 10-fold cross-validated support vector regression in a sample of 780 youth, the multivariate pattern of connectivity from the network defined in A can be used to accurately estimate an individual's age. All panels adapted from Satterthwaite et al., 2013 (Ref 13).

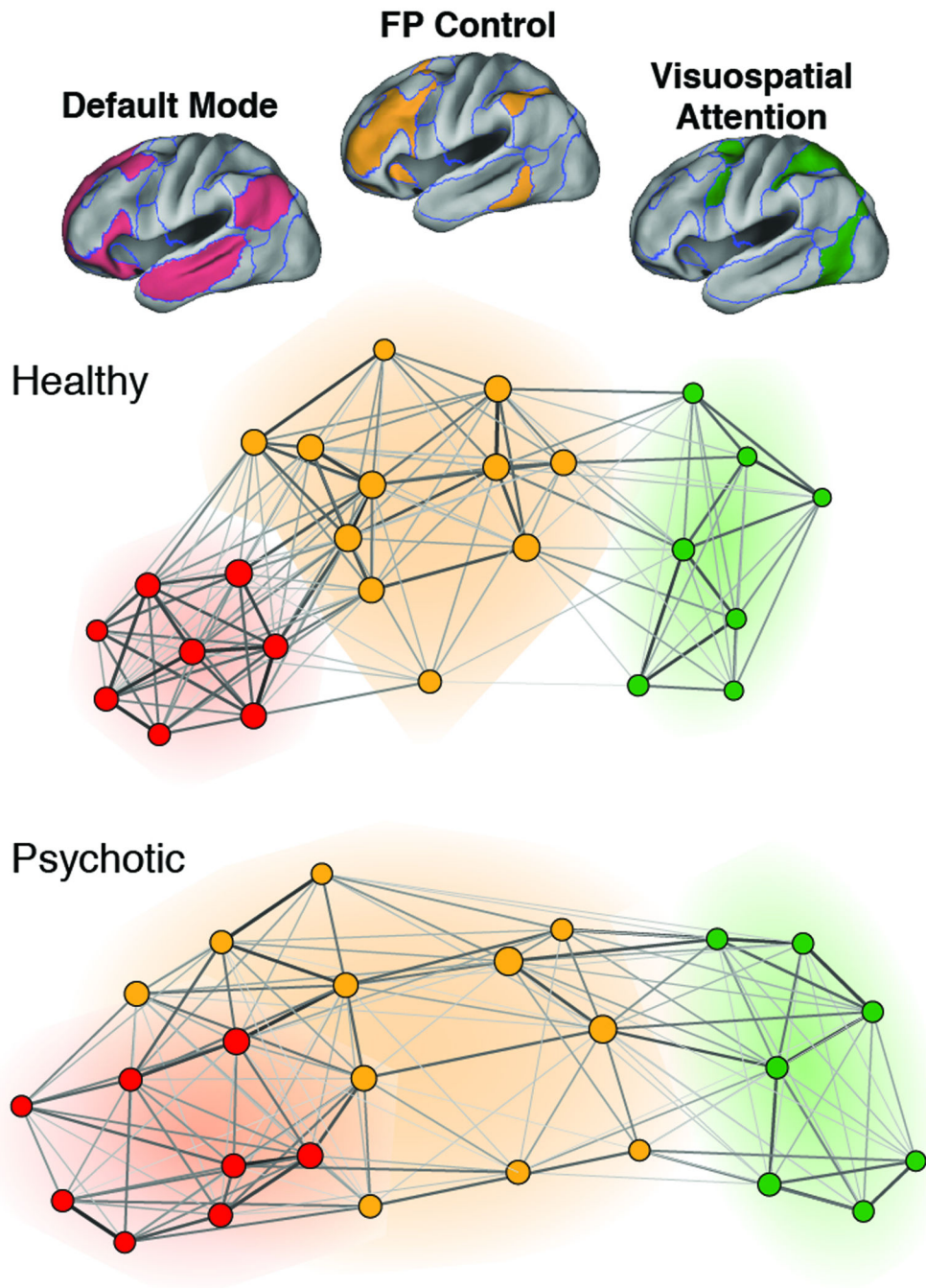


Figure 2. Variation in and among large-scale association networks in chronic psychosis
 Weighted graphs derived from groupwise regional BOLD time course correlations between selected nodes (i.e. cortical regions) of the frontoparietal control network (orange), visuospatial attention network (green), and default network (red) in healthy (n=100, upper panel) and psychotic individuals (n=100, lower panel). Healthy adults showed clear segregation between FP control and default networks (represented with non-overlapping orange and red halos), while patients with chronic psychotic illness showed less clustering

within default and frontoparietal control networks and evidence of extension of FP control nodes into the default cluster (red-orange halo). Adapted from Baker et al., 2104 (Ref 21).