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Original Article

ORIGINAL ARTICLE

Large-Scale Network Topology Reveals Heterogeneity in Individuals With at Risk Mental State for Psychosis: Findings From the Longitudinal Youth-at-Risk Study

Chenhao Wang[1], Jimmy Lee[2], New Fei Ho[1,2], Joseph K.W. Lim[1], Joann S. Poh[1], Gurpreet Rekhi[2], Ranga Krishnan[1], Richard S.E. Keefe[3], R. Alison Adcock[3,4], Stephen J. Wood[5,6], Alex Fornito[7], Michael W. L. Chee[1] and Juan Zhou[1,8]

[1]Center for Cognitive Neuroscience, Neuroscience and Behavioral Disorder Program, Duke-NUS Medical School, National University of Singapore, Singapore 169857, Singapore, [2]Research Division, Institute of Mental Health, Singapore 539747, Singapore, [3]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC 27710, USA, [4]Center for Cognitive Neuroscience, Duke University, Durham, NC 27710, USA, [5]School of Psychology, University of Birmingham, Edgbaston B152TT, UK, [6]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Parkville VIC 3050, Australia, [7]Monash Clinical and Imaging Neuroscience, School of Psychology and Psychiatry & Monash Biomedical Imaging, Monash University, Clayton VIC 3800, Australia and [8]Clinical Imaging Research Centre, The Agency for Science, Technology and Research and National University of Singapore, Singapore 117599, Singapore

Address correspondence to Dr Juan Zhou, Center for Cognitive Neuroscience, Neuroscience & Behavioral Disorders Program, Duke-NUS Medical School, 8 College Road, #06-15, Singapore 169857, Singapore. E-mail: helen.zhou@duke-nus.edu.sg

Abstract

Emerging evidence demonstrates heterogeneity in clinical outcomes of prodromal psychosis that only a small percentage of at-risk individuals eventually progress to full-blown psychosis. To examine the neurobiological underpinnings of this heterogeneity from a network perspective, we tested whether the early patterns of large-scale brain network topology were associated with risk of developing clinical psychosis. Task-free functional MRI data were acquired from subjects with At Risk Mental State (ARMS) for psychosis and healthy controls (HC). All individuals had no history of drug abuse and were not on antipsychotics. We performed functional connectomics analysis to identify patterns of system-level functional brain dysconnectivity associated with ARMS individuals with different outcomes. In comparison to HC and ARMS who did not transition to psychosis at follow-up (ARMS-NT), ARMS individuals who did (ARMS-T) showed marked brain functional dysconnectivity, characterized by loss of network segregation and disruption of network communities, especially the salience, default, dorsal attention, sensorimotor and limbic networks ($P < 0.05$ FWE-corrected, Cohen's $d > 1.00$), and was associated with baseline symptom severity. In contrast, we did not observe connectivity differences between ARMS-NT and HC individuals. Taken together, these results suggest a possible large-scale functional brain network topology phenotype related to risk of psychosis transition in ARMS individuals.

Key words: at risk for psychosis, brain connectomics, functional connectivity, LYRIKS, transition to psychosis

Introduction

The clinical diagnosis of psychosis is preceded by a prodromal stage in which the individual experiences brief or attenuated psychotic symptoms and a decline in functioning (Fusar-Poli et al. 2013). Individuals with At Risk Mental State (ARMS) for psychosis are identified using psychometric interviews, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al. 2005). While some ARMS individuals transition to psychosis, most of them do not (Fusar-Poli et al. 2015). Accordingly, spontaneous symptomatic remission occurs in ARMS individuals. Under the framework of the neurodevelopment hypothesis of schizophrenia, it has been argued that the individual heterogeneity in inherent brain circuitries precipitates differences in later life outcomes. Identifying the neurobiological features that explain the heterogeneous clinical course in ARMS individuals is important to understand the pathogenic mechanisms of psychosis and could potentially lead to better screening assessments for preclinical schizophrenia. In particular, early detection of preclinical psychosis offers the window of opportunity for potential behavioral and pharmacological intervention to potentially delay or prevent the progression to severe psychosis (McFarlane et al. 2015).

Several studies have reported cross-sectional and longitudinal differences between the ARMS subgroup that transitions to psychosis (ARMS-T) and the ARMS subgroup that does not transition to psychosis (ARMS-NT) with respect to psychometric measures (Johnstone et al. 2005), gray (Cannon et al. 2015) and white matter (WM) volumes (Bloemen et al. 2010), dopamine synthesis capacity (Howes et al. 2011) and task-related neural activities and connectivity (Sabb et al. 2010). Although these studies identified risk factors linked to the onset of psychosis, many have reported weak to moderate effect sizes. Antipsychotic medications and substance abuse which have been shown to affect brain structure and function in psychosis may have contributed to these weak findings (Liao et al. 2012; Fusar-Poli et al. 2015).

Our recent work found no reductions in gray matter volume or cortical thickness between ARMS-T, ARMS-NT and HC individuals at baseline after excluding these confounders (Klauser et al. 2015), although this group did show reductions in corticostriatal functional connectivity (FC) that mirror those seen in patients with psychosis (Fornito et al. 2013; Dandash et al. 2014), suggesting that FC may be a more sensitive marker of early brain changes in psychosis. While this is consistent with an emerging consensus that psychosis arises from disrupted communication between distributed neural systems (Fornito et al. 2012), little is known about whether these observed FC abnormalities in ARMS individuals were related their clinical outcomes. Accordingly, resting state functional connectivity, which is used to analyze statistical dependencies in fluctuations in functional MRI signals in subjects under task-free conditions has emerged as a key approach to evaluating large-scale functional networks (Fox and Raichle 2007).

Recent resting FC studies have reported widespread functional dysconnectivity in psychosis, targeting multiple neural systems that include the frontal regions, auditory cortex, default mode network (DMN; posterior cingulate cortex, medial prefrontal cortex, angular gyrus and medial temporal cortex; refer Supplementary Table 1 for complete list of brain region in the network), thalamocortical circuits and salience network (SN; anterior cingulate cortex and frontoinsular cortex; Supplementary Table 1) (Palaniyappan and Liddle 2012; Klingner et al. 2014; van den Heuvel and Fornito 2014). FC disruptions in psychosis are also associated with more severe symptoms and more cognitive impairments (Fornito et al. 2013). While similar observations of FC disruptions were reported in ARMS individuals (Shim et al. 2010; Dandash et al. 2014; Wang et al. 2016), it is still unclear whether the abnormalities can be further differentiated between those who transition into full-blown psychosis and those who do not. One recent study performed a focused examination of the thalamocortical circuits and found functional dysconnectivity between the thalamus and multiple cortical regions in ARMS-T individuals (Anticevic et al. 2015). Given the evidence that psychosis targets widely distributed functional networks (Pettersson-Yeo et al. 2011), it is possible that the FC disruptions that predict the transition to psychosis in ARMS individuals involve multiple pathways. Therefore, it is important to extend the current literature by adopting a whole-brain connectome-wide approach in examining FC integrity. To this end, graph theory has been recently applied in functional connectomics analysis to elucidate the organization of complex networks at the regional and system levels (Newman 2006; Bullmore and Sporns 2009). For example, examining the large-scale functional network organization, we revealed that a healthy functional network topology predicted regional neural abnormalities in brain disorders (Zhou et al. 2012). Importantly, graph theoretical studies have found network abnormalities such as reduced network communication efficiency, disrupted local clustering, and altered network architectures in psychosis (van den Heuvel et al. 2010; Micheloyannis 2012; Lo et al. 2015).

However, whether and how large-scale brain network FC contributes to the heterogeneous transition risk in ARMS individuals remains largely unknown. To close this gap, the present work analyzed the baseline task-free functional MRI data of a large sample of healthy controls (HC) and ARMS individuals that were subtyped into ARMS-T and ARMS-NT groups according to their follow-up status. All individuals had no history of illicit substance use and were not on antipsychotic medications. Rather than adopting a candidate circuits approach, we conducted whole-brain connectome-wide analyses to examine FC differences among the 3 groups. Specifically, we investigated the FC strengths of predefined whole-brain regions and then applied graph theoretical analysis to examine group differences in 2 network topology metrics: efficiency, which measures how easy it is for nodes to exchange information in the network (Bullmore and Sporns 2009), and the clustering coefficient, which quantifies the tendency of small subsets of nodes to interconnect with each other in cliquish groups (Watts and Strogatz 1998). To understand the extent of FC disruptions on the system-level network architecture (Newman 2006), we subsequently examined the group differences in network community structures. We hypothesized that the heterogeneity in psychosis outcome would be evidenced by differential disruptions of baseline FC features in the ARMS subgroups compared with the controls. Specifically, the ARMS-T subjects (but not the ARMS-NT subjects) would show extensive reductions in efficiency and the clustering coefficient in multiple neural networks. Moreover, ARMS-T individuals would exhibit an aberrant network community structure that deviates from the organization of the healthy brain. In addition, we expected the extent of FC disruptions in ARMS-T individuals to be associated with the baseline symptoms severity.

Methods

Participants

We studied 88 young ARMS individuals and 48 age-, gender-, and handedness-matched HC participants. The data were

collected as part of the Longitudinal Youth-at-Risk Study (2008–2015 in Singapore) (Lee et al. 2013; Klauser et al. 2015). Participants recruitment follows the criteria as described in the early work (Wang et al. 2016) (see Supplementary Methods). Individuals in the ARMS group met the specific criteria of the CAARMS (Yung et al. 2005) and were excluded from the study if they had a history of a medical disorder that might cause psychosis, were diagnosed with mental retardation, were taking antipsychotic medications or had a history of illicit substance. Ethics approval for this study was provided by the National Healthcare Group's Domain-Specific Review Board. Of the 88 ARMS participants, 48 were taking prescription antidepressants, 3 were taking benzodiazepines, and 71 had a comorbid depressive and/or anxiety disorder. HCs, which had no history of neuropsychiatric disorders, family history of psychosis in a first-degree relative, or substance abuse/dependency, were recruited from the local community. All HCs were ARMS negative as assessed using the CAARMS. All participants were reimbursed for their time.

Clinical Measures and Psychosis Transition in ARMS Individuals

All participants were followed up longitudinally from 2008 to the fall of 2015. The CAARMS and PANSS were administered to the ARMS participants every 12 months until the point of transition to clinical psychosis. The ARMS subjects were assigned to 1 of 2 groups according to their longitudinal clinical assessment, namely ARMS subjects who transitioned to psychosis (ARMS-T) during the course of the study and those who did not transition to psychosis (ARMS-NT), which was determined using the structured clinical interview for DSM-IV Axis I Disorders (Lee et al. 2013).

MRI Acquisition and Imaging Processing

The participants underwent 1 neuroimaging session on a 3 T Siemens Tim Trio system (Siemens, Erlangen, Germany) with a 12-channel head coil. High-resolution T1-weighted images was acquired using a T1-weighted 3D magnetization-prepared rapid-acquisition gradient echo sequence (TR/TE = 2300/3 ms, FOV = 256 × 256 mm^2, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm^3, 192 slices with 1 mm slice thickness, slice gap = 0.5 mm). A 6-min task-free T2*-weighted fMRI scan was acquired using a gradient echo-planar imaging sequence (TR/TE = 2000/30 ms, TA = 90°, FOV = 192 × 192 mm^2, matrix size = 64 × 63, voxel size = 3 × 3 × 3 mm^3, 36 slices with 3 mm slice thickness, slice gap = 0 mm; the participants were instructed to close their eyes and not fall asleep). The task-free fMRI data were preprocessed using procedures described in our previous studies (Wang et al. 2016), including a motion scrubbing that discarded fMRI volumes with frame displacement > 0.2 mm and variance of temporal derivative of time courses over voxels >0.3% (Power et al. 2012) (see Supplementary Methods).

Whole-Brain Connectome-Wide FC Strength Analysis

To estimate the whole-brain FC strengths, we extracted the mean fMRI time course in each of the 144 predefined regions of interest (ROIs) (Tzourio-Mazoyer et al. 2002; Yeo et al. 2011) over the entire 6-min task-free scan (see Supplementary Methods). For each subject, the FC matrix representing the pairwise associations between the 144 ROIs was computed using Pearson's correlation coefficient. Following Fisher's z transformation, group differences in the FC strengths were identified using a 2-sample *t*-test with a threshold of $P < 0.05$ FWE corrected via the Bonferroni method (same for all FWE results reported in this work) after controlling for age and gender.

Graph Theoretical Analysis

We performed graph theoretical analysis to compare the network topological properties between the ARMS-T, ARMS-NT, and HC groups (Bullmore and Sporns 2009). To evaluate network integration and segregation, group differences in 2 graph theoretical metrics at the global and nodal levels (efficiency and clustering coefficients, respectively) (Rubinov and Sporns 2010), were evaluated using pairwise 2-sample *t*-tests thresholded at $P < 0.05$ FWE-corrected, after controlling for age and gender (see Supplementary Methods). To derive group-level network community structures, we performed a 2-stage consensus community detection within each group following the methods described previously (Lancichinetti and Fortunato 2012) (see Supplementary Methods).

Correlation of FC Disruptions in ARMS-T With Concurrent Symptom Severity

To assess the relationships between the FC disruptions and symptom severity at baseline, we correlated network-level nodal efficiencies with CAARMS total severity score, that is, the sum of the scores across all the CAARMS subscales, as well as the PANSS positive, negative and general psychopathology scores ($P < 0.05$). The network-level nodal efficiencies were the mean nodal efficiencies of brain regions in 6 functional networks as defined in a previous study (Yeo et al. 2011). Only brain regions that revealed significant group differences between ARMS-NT individuals and ARMS-T individuals were used.

Results

Participant Characteristics

There were no differences in age, gender, handedness, ethnicity, and motion parameters (both maximum and mean of absolute displacement) among the HC, ARMS-NT, and ARMS-T groups ($P < 0.05$, Chi-square test and one-way ANOVA for discrete and continuous variables respectively, Table 1). Of the 88 ARMS subjects, 12 developed frank psychosis over the course of this study. The median time from the baseline scan to conversion was 11.5 months (mean = 17 ± 13 months). There were no group differences in medication use at baseline (i.e., antidepressants or benzodiazepines) or depressive or anxious comorbidities and the baseline symptom severity scores between the ARMS-NT and ARMS-T groups ($P < 0.05$, 2-sample *t*-tests, Table 1).

FC Strengths and Topological Properties at Baseline Associated With Differential Psychosis Outcomes

The ARMS-T individuals exhibited widespread internetwork and intranetwork functional connectivity reductions at baseline compared with the HC ($P < 0.05$ FWE-corrected, Cohen's $d > 1.40$, Fig. 1 left). The functional connectivity reductions in the ARMS-T group were mostly along connections that involved the limbic system, particularly the hippocampus and amygdala; the posterior/dorsal part of the default mode network involving the precuneus and posterior cingulate cortex;

Table 1. Characteristics of ultra-high risk individuals who transitioned to psychosis (ARMS-T), those who did not transition (ARMS-NT) and healthy controls (HC) in task-free fMRI functional connectivity analysis.

	HC		ARMS-NT		ARMS-T		Test statistics	
	(N = 48)		(N = 76)		(N = 12)		Chi-square	P
	N	%	N	%	N	%		
Male	23	48	50	66	9	75	5.11	0.078
Handedness								
Right	42	88	65	86	10	83	0.18	0.916
Left	2	4	5	7	2	17	2.43	0.297
Mixed	4	8	6	8	0	0	0.79	0.673
Ethnicity								
Chinese	26	54	53	70	9	75	3.73	0.155
Malay	12	25	16	21	3	25	0.30	0.862
Indian	8	17	5	7	0	0	4.85	0.088
Other	2	4	2	3	0	0	0.54	0.765
Medication	–	–	43	57	8	67	0.43	0.511
Comorbidity								
Depressive	–	–	58	76	12	100	3.57	0.059
Anxious	–	–	27	36	5	42	0.17	0.681
	Mean	SD	Mean	SD	Mean	SD	F tests	P
Age (years)	21.5	4.2	21.7	3.6	19.7	3.1	1.45	0.237
Head motion parameters								
Mean abs. displacement	0.20	0.12	0.20	0.15	0.22	0.17	0.09	0.914
Max abs. displacement	0.59	0.56	0.56	0.43	0.87	1.03	1.61	0.205
			Mean	SD	Mean	SD	T tests	P
PANSS								
Positive score	–	–	10.8	2.8	11.8	3.3	−1.18	0.242
Negative score	–	–	12.1	4.1	13.2	3.9	−0.81	0.419
General score	–	–	25.4	6.7	28.1	8.6	−1.24	0.219
Total CAARMS score	–	–	24.5	15.6	29.1	13.9	−0.96	0.340

*Selective serotonin reuptake inhibitors (SSRIs) antidepressants.

F tests and $\chi 2$ tests were used to assess group differences in continuous and discrete variables, respectively. *T*-tests were used to compare differences between the ARMS-NT and ARMS-T groups.

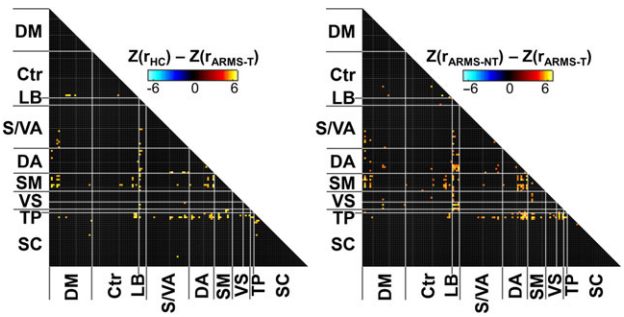

Figure 1. Reduced functional connectivity strengths at baseline closely predict the transition to psychosis in ultra-high risk individuals. *Left*: A similar pattern of FC reductions in the ARMS-T group was observed compared with healthy controls (HC) ($P < 0.05$ FWE corrected, Cohen's $d > 1.40$). *Right*: Reduced functional connectivity (FC) strengths in ultra-high risk individuals who transitioned to psychosis (ARMS-T) compared with those did not transition (ARMS-NT) ($P < 0.05$ FWE corrected, Cohen's $d > 1.26$). No group differences in FC strengths were identified between the HC and ARMS-NT groups. All analyses controlled for age and gender. Key: DM = default mode network; Ctr = executive control network; LB = limbic system; S/VA = salience/ventral attention network; DA = dorsal attention network; SM = somatosensory and motor network; VS = visual network; TP = temporal parietal network; SC = subcortical regions.

the insular region of the salience. A similar pattern of functional connectivity reductions was observed in the comparison between the ARMS-T and ARMS-NT groups ($P < 0.05$ FWE-corrected, Cohen's $d > 1.26$, Fig. 1 right). In contrast, no group differences were observed between the ARMS-NT and HC.

Compared with the ARMS-NT individuals, the ARMS-T individuals exhibited reduced global efficiency at baseline ($P < 0.05$ FWE-corrected, t-stats = 4.45, Cohen's $d = 1.33$, Fig. 2 top left). Further examinations indicated that the global differences were due to focal reductions of nodal efficiencies in regions including the insula, central and peripheral visual cortex, posterior parietal cortex and somatosensory and motor cortex ($P < 0.05$ FWE-corrected, t-stats > 4.42, Cohen's $d > 1.00$, Fig. 2 bottom left, Supplementary Table S2). Similarly, the clustering coefficients were reduced in the ARMS-T group compared with the ARMS-NT group at both the global level ($P < 0.05$ FWE-corrected, t-stats = 4.42, Cohen's $d = 1.29$, Fig. 2 top right) and the nodal level (Supplementary Table S3). Comparisons of the efficiency and clustering coefficients between the ARMS-T and HC revealed similar findings at both the global and nodal levels (Fig. 2 bottom right and Supplementary Tables S4 and S5). In contrast, there were no topological differences between the ARMS-NT individuals and the HC. These findings remained after controlling for the effects of medications, comorbidities and regional gray matter volumes. To examine if the group differences in network topology could be due to gray matter loss, we repeated the global and nodal group differences analysis controlling for the whole-brain and regional gray matter volume, respectively. These results remained largely unchanged (Supplementary Tables S6 and S7).

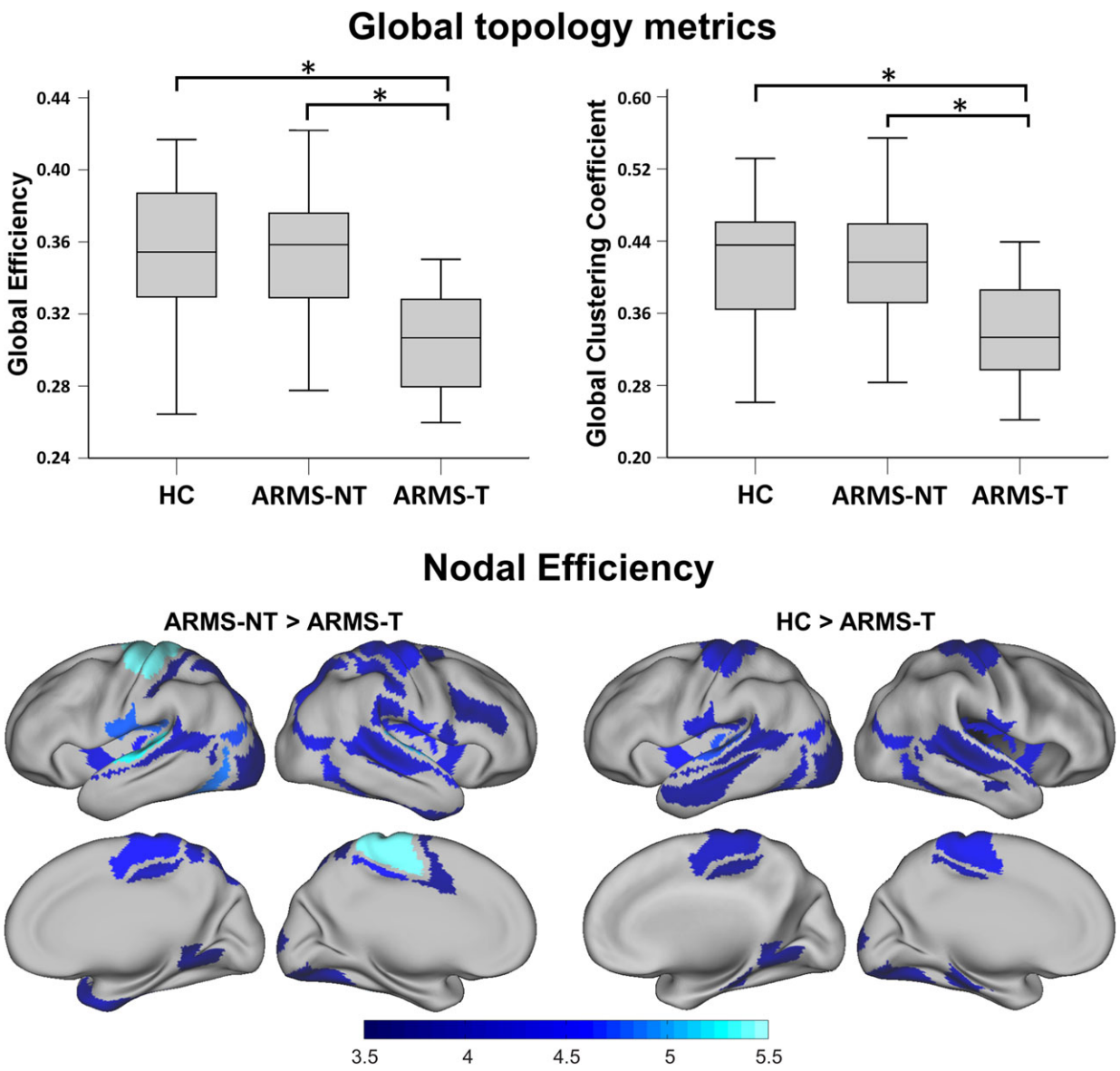

Figure 2. Reduced topological properties at baseline in ultra-high risk individuals who transitioned to psychosis (ARMS-T) compared with those who did not transition (ARMS-NT) and healthy controls (U S AHC). *Top*: Box plots showing the global efficiency coefficient (top left) and global clustering coefficient (top right) among ARMS-T, ARMS-NT and HC groups (*$P < 0.05$ FWE corrected). *Bottom*: brain surface plots indicating regions of reduced nodal efficiency between ARMS-T and ARMS-NT individuals (bottom left) and between HCs and ARMS-T individuals (bottom right) ($P < 0.05$ FWE corrected). The findings of subcortical regions are not shown in the surface plots but are presented in Supplementary Tables S2 and S3. All analyses controlled for age and gender.

Altered Functional Network Organization in ARMS-T But not in ARMS-NT

At the whole-brain level, the network community structures of the ARMS-NT group were similar to those of the HC (Adjusted Rand Index (Rand 1971)), a measure of partition similarity = 0.845, Fig. 3 left and middle). The community blocks in both groups largely agreed with the labeling of networks in the graph (Yeo et al. 2011) which represents the widely accepted descriptions of brain functional organization in the literature on human functional connectomes (Power et al. 2011).

In contrast, the community structure in the ARMS-T group (Fig. 3 right) displayed a distinct pattern from that of the HC and ARMS-NT groups, reflecting extensive reorganizations of the network community structure, as evidenced by a low Adjusted Rand Index of 0.345 and 0.377, respectively. This extensive reorganization was characterized by the following. First, instead of forming one community with the dorsal attentional network (intraparietal sulcus and frontal eye fields; Supplementary Table S1) in health, the control network merged with the DMN into one community in ARMS-T. Second, there were significant breakdowns in the SN community; namely, part of the SN regions (ventral lateral prefrontal cortex and inferior parietal lobule) was included in the DMN-control community, whereas the orbital-frontal part (medial posterior prefrontal cortex and ventral prefrontal cortex) of the SN was incorporated into the community of the striatum. Third, the visual network extended to the limbic system (including hippocampus and amygdala) and part of the dorsal attention network (occipital/temporal cortex, occipital/parietal cortex and superior parietal lobule).

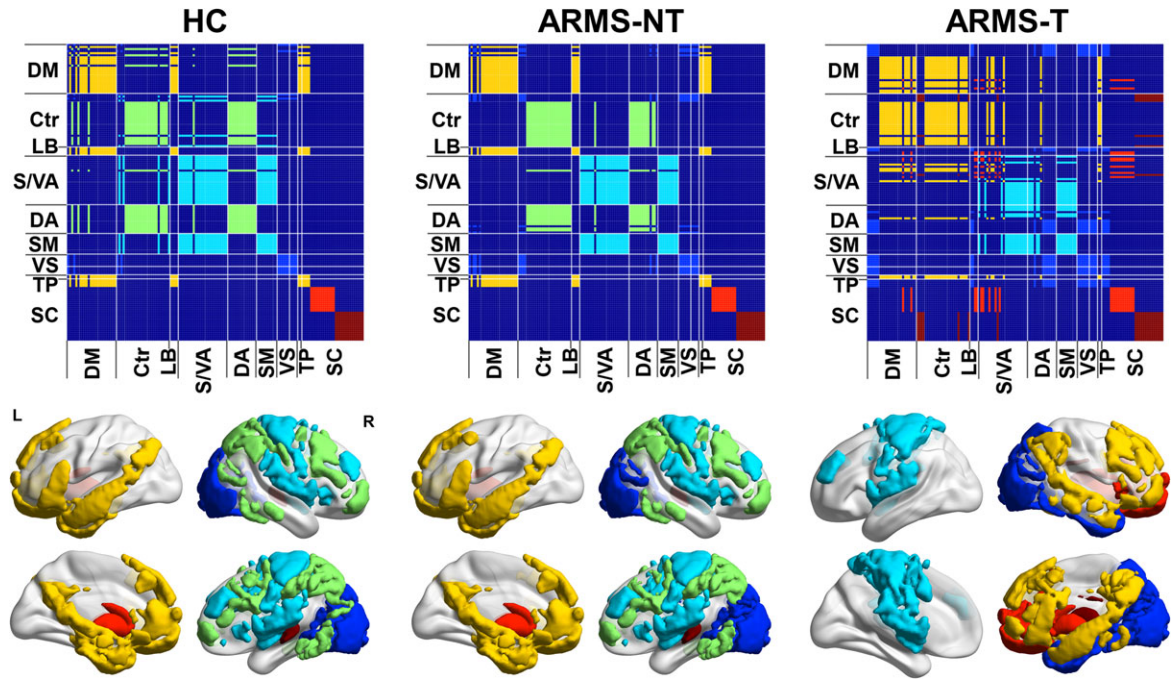

Figure 3. Altered network architecture in ultra-high risk individuals who transitioned to psychosis (ARMS-T). *Top*: consensus matrices showing community structures in each of the 3 groups (HC, ARMS-NT and ARMS-T). The edges connecting nodes in the same community are highlighted using the same color. *Bottom*: anatomical locations of detected communities. The same color themes were applied as in the corresponding consensus matrices above. Key: DM = default mode network, Ctr = executive control network, LB = limbic system, S/VA = salience/ventral attention network, DA = dorsal attention network, SM = somatosensory and motor network, VS = visual network, TP = temporal parietal network, SC = subcortical regions.

Disruptions in Functional Network Integrity Associated With Concurrent Symptom Severity

In the SN, the mean nodal efficiency computed over regions that were reduced in the ARMS-T group was associated with the baseline PANSS general scores ($P < 0.05$ FWE-corrected, $r^2 = 0.666$, Fig. 4, top left panel). Similar associations were found (1) between the mean nodal efficiency of the SN and baseline PANSS negative/total scores; (2) between the mean nodal efficiency of the dorsal attention and executive control network (dorsal lateral prefrontal cortex, ventrolateral prefrontal cortex and lateral parietal cortices; Supplementary Table S1) and baseline PANSS general, negative and total scores; and (3) between the mean nodal efficiency of visual and somatosensory/motor network and PANSS negative scores ($P < 0.05$ uncorrected, Fig. 4, Supplementary Table S8). In contrast, none of these associations were significant in the ARMS-NT group. No associations were found between nodal efficiencies and PANSS positive scores in either ARMS-T or ARMS-NT groups.

Discussion

We found no group differences in FC between the ARMS-NT and HC groups. In contrast, compared with the ARMS-NT and HC groups, the ARMS-T group had baseline reductions in FC strengths and topological properties involving multiple specific large-scale brain networks, including the SN, dorsal attention network, default mode network, sensorimotor network, and limbic system. These FC disruptions were not explained by gray matter volume loss and were associated with the severity of symptoms in ARMS-T individuals. Collectively, these regional FC changes in ARMS-T individuals led to the reorganization of network architecture characterized by a loss of segregation among functionally specialized neural systems as well as disruptions of network communities. To our knowledge, this is the first study examining the large-scale functional network architecture in ARMS individuals with no history of illicit substance use and who were free of antipsychotic medications. These findings suggest that the degree of brain functional network dysconnectivity could underlie the differences in later life symptomatic outcomes.

Heterogeneity in the ARMS Group and Its Neurobiological Basis

Is the ARMS state a single pathological condition preceding clinical psychosis, or is it a mixture of distinct pathological states? Our findings revealed that pronounced heterogeneity within the ARMS population in terms of the connectivity strength and organization of brain functional networks, thus supporting the latter hypothesis. Whereas FC integrity in the ARMS-T group was markedly disrupted compared with that of the HC group, these changes were absent in the ARMS-NT group. Neuroimaging features that demarcate the ARMS-T subgroup from other ARMS individuals could be the neurobiological mechanisms explaining the heterogeneity in the ARMS cohort. The present study has 2 implications in the field of prodromal psychosis. First, the current selection criteria for at-risk individuals, such as the CAARMS, are based on psychometric assessment alone. In practice, the performances of these screening methods could be compromised due to issues such as the difficulty of detecting subthreshold and nonspecific signs of prodromal psychosis that may also share overlapping symptoms with other psychiatric conditions. The inclusion of objective biological measurements, such as the imaging connectomics described in this work, could help stratify psychosis risk and improve the

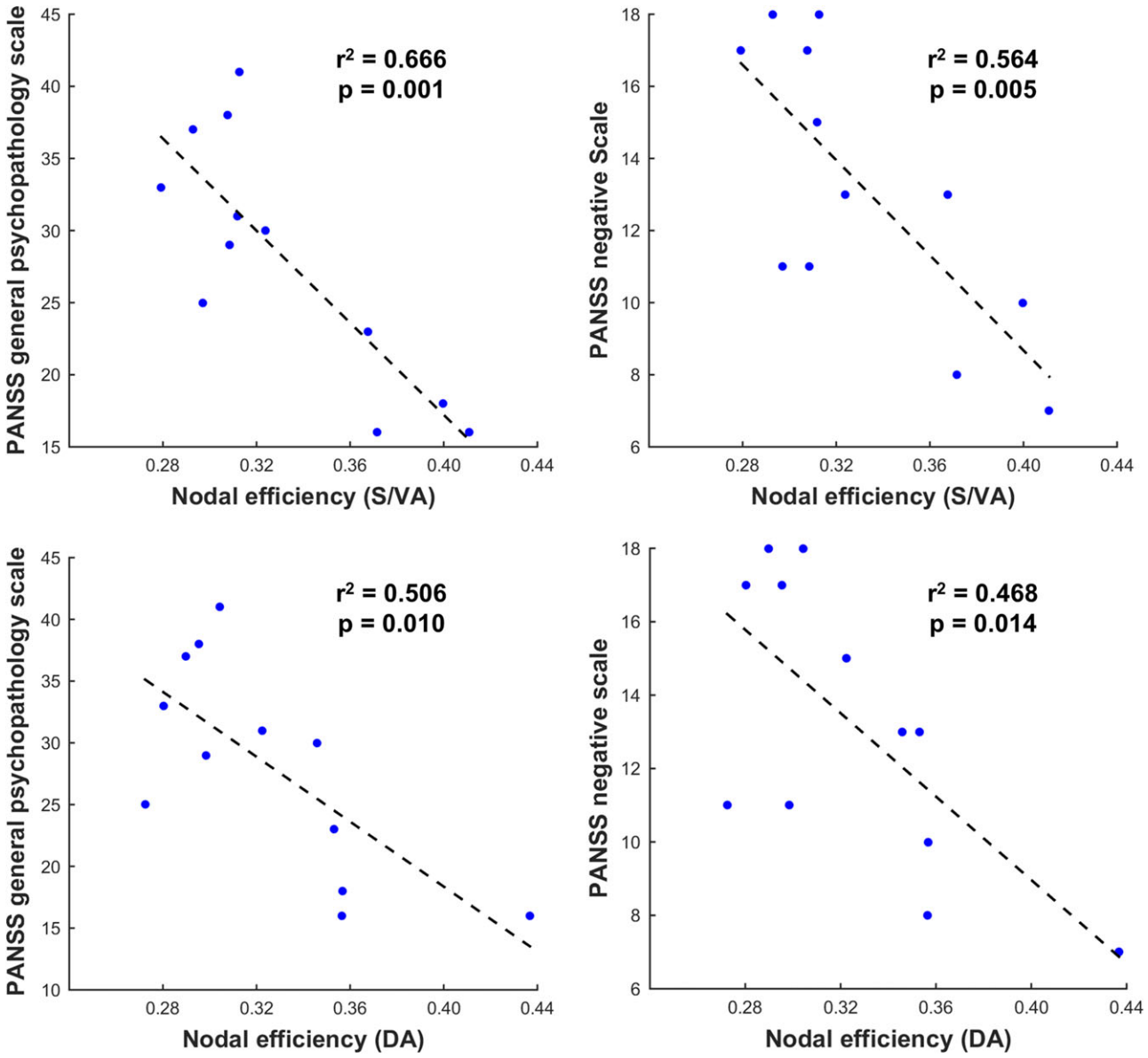

Figure 4. Functional connectivity disruptions correlate with symptom severity. Clinical severity as evaluated by PANSS negative and general scores was negatively associated with the mean nodal efficiency of the salience/ventral attention network and dorsal attention network in individuals identified as ultra-high risk who transitioned to psychosis (ARMS-T) ($P < 0.05$). Only regions that indicated group differences between ARMS-T individuals and ARMS-NT individuals were used in the analysis.

performance of screening protocols. Second, the lack of group differences between the ARMS-NT and HC groups highlights the importance of the conversion status in studies of individuals at-risk for psychosis. Cross-sectional studies examining ARMS individuals as a single group may result in missing important brain structural and functional changes that are exclusive in AMRS-T individuals. Thus, interpretations of the findings from the ARMS group should consider their follow-up status.

Network Topology Disruptions in ARMS-T Targeting Multiple Networks

In this study, the analysis of nodal efficiency revealed localized FC disruptions associated with the onset of psychosis in ARMS individuals in regions corresponding to the bilateral insular cortex, the posterior part of the dorsal attention network, the sensorimotor network including the auditory cortex, the hippocampus, and the limbic system. The involvement of these functional networks in psychosis has been highlighted in previous studies. For example, the insula is regarded as the hub of the proximal SN, which is a critical neural system involved in the detection and processing of salient information (Menon and Uddin 2010). Aberrant insular connectivity of the proximal SN has been found in psychotic patients (Zhou et al. 2007) and is hypothesized to be a neural mechanism that leads to psychotic symptoms (Palaniyappan et al. 2013). In addition to studies reporting a similar pattern of insular dysconnectivity in prodromal psychosis (Dandash et al. 2014; Wang et al. 2016), the present work showed that these changes are directly associated to psychosis transition. The findings from our study also parallel those of a recent FC analysis which reported reduced within- and between-network connectivity involving somatosensory

and motor regions in childhood-onset schizophrenia (Berman et al. 2016). Similarly, the involvement of other systems in the association cortices corresponds to the observation that psychosis affects multiple cognitive domains (Dickinson et al. 2004). These phenotypic abnormalities may be related to the dysconnectivity of the corresponding functionally specialized networks and the interactions among these systems (Pettersson-Yeo et al. 2011; van den Heuvel and Fornito 2014).

Because the FC disruptions were observed across multiple brain networks and involved both internetwork and intranetwork functional connections, it is not surprising that the network community structures in ARMS-T individuals were markedly different from the expected patterns of functional organization in the healthy brain. The network reorganizations in the ARMS-T group are characterized by both the disintegration of specific network communities and the loss of segregation among functional systems. Specifically, our findings suggest that part of the SN, notably the regions in the orbitofrontal cortex (OFC), loses its association with other parts of the SN and develops connections to the striatum, forming one community. Increased dopaminergic transmission in striatum is one the most robust pathophysiological features in psychosis and is closely coupled to the abnormal prefrontal activity that underlies cognitive impairments in the ARMS individuals (Fusar-Poli et al. 2010). To understand the biochemical basis of the present result, dopamine-sensitive neuroimaging imaging techniques (Elsinga et al. 2006; Egerton et al. 2013) could be used to examine whether the increased association between the striatum and the frontal regions were related to elevated dopamine synthesis and transmission in the striatum (Howes et al. 2009, 2011). Furthermore, the brain regions in ARMS-T individuals that formed the backbone of the DMN (Greicius et al. 2003) no longer stand as an independent community but merge with several prefrontal regions corresponding to the executive control network (Seeley et al. 2007). The loss of segregation between the DMN and task-positive networks is a prominent feature of neuropsychiatric disorders (Manoliu et al. 2014; Wotruba et al. 2014). This is consistent with findings of task-related hyperactivity and hyperconnectivity of the DMN (Whitfield-Gabrieli et al. 2009) accompanied by hypoactivity in regions of task-positive networks (Pomarol-Clotet et al. 2008). Abnormal connectivity between cortical regions and subcortical structures, such as the thalamus, has been highlighted in several studies as the key feature of brain dysconnectivity in psychosis (Klingner et al. 2014) and has been used as the biomarker to predict psychosis transition in ARMS individuals (Anticevic et al. 2015). In the present study, we found significantly reduced nodal efficiency in a thalamus cluster among ARMS-T individuals compared with HCs. A similar trend in the same regions, despite not surviving multiple comparison corrections, was observed in the comparison between the ARMS-T and ARMS-NT groups. In addition, the thalamus, hippocampus, and amygdala revealed a widespread reduction in the nodal clustering coefficient in ARMS-T individuals compared with both the HC and ARMS-NT individuals (Supplementary Tables S3 and S5). Many of these regions are part of the limbic system, which consists of important neural substrates that regulate emotions and has been implicated in the pathophysiology of psychosis.

Functional Dysconnectivity Associated With Baseline Symptom Severity and Later Psychosis Risk in ARMS Individuals

In line with previous studies reporting FC changes predate the onset of frank psychotic symptoms (Wang et al. 2016), we identified key FC topological changes at baseline in ARMS-T individuals that were absent in ARMS-NT individuals. Despite the limited sample size of the ARMS-T subgroup, the effect sizes of these findings were remarkable. Therefore, in addition to the many risk factors that have been studied to predict the onset of psychosis (Cannon et al. 2016), the present study suggests that further developed, neurobiological features extracted from functional imaging connectomics could also shed light on the disease progression in prodromal psychosis. Moreover, it is not likely that our findings were confounded by substance use or antipsychotic medications, and the results remained the same after controlling for the effects of medications and/or comorbidities. The patterns of FC disruptions were consistent with the multidimensional nature of psychosis that affects several psychocognitive domains. Importantly, the extent of network disruptions was correlated with symptom severity scores in the ARMS-T subgroup specifically, suggesting these FC abnormalities could be related to the symptomatology of prodromal psychosis.

Limitations and Conclusion

An unavoidable consequence of multiregion whole-brain functional connectivity analyses is the issue of multiple comparisons. To minimize false positives, we performed Bonferroni corrections to control for the multiple comparisons using the total number of pairwise connections or brain regions. More importantly, we performed graph theoretical analyses from connection to node and to the global structure. This approach progressively reduces the dimensionality of the analysis and allows us to systematically determine if the patterns of network disruptions are preserved across all levels. Secondly, the findings of functional dysconnectivity in ARMS-T individuals should be interpreted with caution because of the limited sample size. This is a common issue in most single-site ARMS studies that have investigated the transition to psychosis among ARMS individuals. The challenges in recruiting subjects from the community and completing clinical follow-ups combined with the apparent declining transition rate in recent studies mean that a large number of ARMS participants must be recruited at baseline to produce an adequate number of ARMS-T subjects after years of follow-up. Further validations using large longitudinal samples via a multisite collaborative study, particularly correlating baseline neuroimaging features and changes in behavioral measures before and after psychosis transition (Hengartner et al. 2017), are needed. Also, the lack of group difference between ARMS-NT and HC individuals could be partly due to the group heterogeneity. Future studies examining ARMS-NT subgroups might be able to identify phenotype specific connectivity abnormalities. Technically, fMRI signal loss and distortion is a potential issue in brain regions near air–tissue interface (Ojemann et al. 1997) and could be minimized by MR methods such as field map correction in future studies. Similarly, movement-related artifacts and physiological noise in fMRI dataset could be further corrected by implementing advanced fMRI preprocessing techniques (Caballero-Gaudes and Reynolds 2017).

Taken together, the results of this study showed that functional dysconnectivity was associated with variable outcomes in at-risk individuals and could be an important component of the underlying neural mechanism of psychosis. The characterization of brain dysconnectivity in psychosis using neuroimaging connectomics could potentially advance the assessment of preclinical psychosis.

Supplementary Material

Supplementary data is available at *Cerebral Cortex* online.

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Notes

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