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Archival Report

Dysregulated Brain Dynamics in a Triple-Network Saliency Model of Schizophrenia and Its Relation to Psychosis

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ABSTRACT

BACKGROUND: Schizophrenia is a highly disabling psychiatric disorder characterized by a range of positive "psychosis" symptoms. However, the neurobiology of psychosis and associated systems-level disruptions in the brain remain poorly understood. Here, we test an aberrant saliency model of psychosis, which posits that dysregulated dynamic cross-network interactions among the salience network (SN), central executive network, and default mode network contribute to positive symptoms in patients with schizophrenia.

METHODS: Using task-free functional magnetic resonance imaging data from two independent cohorts, we examined 1) dynamic time-varying cross-network interactions among the SN, central executive network, and default mode network in 130 patients with schizophrenia versus well-matched control subjects; 2) accuracy of a saliency model–based classifier for distinguishing dynamic brain network interactions in patients versus control subjects; and 3) the relation between SN-centered network dynamics and clinical symptoms.

RESULTS: In both cohorts, we found that dynamic SN-centered cross-network interactions were significantly reduced, less persistent, and more variable in patients with schizophrenia compared with control subjects. Multivariate classification analysis identified dynamic SN-centered cross-network interaction patterns as factors that distinguish patients from control subjects, with accuracies of 78% and 80% in the two cohorts, respectively. Crucially, in both cohorts, dynamic time-varying measures of SN-centered cross-network interactions were correlated with positive, but not negative, symptoms.

CONCLUSIONS: Aberrations in time-varying engagement of the SN with the central executive network and default mode network is a clinically relevant neurobiological signature of psychosis in schizophrenia. Our findings provide strong evidence for dysregulated brain dynamics in a triple-network saliency model of schizophrenia and inform theoretically motivated systems neuroscience approaches for characterizing aberrant brain dynamics associated with psychosis.

Keywords: Brain network dynamics, fMRI, Multivariate classification, Psychosis, Salience network, Schizophrenia

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Schizophrenia is a severe and disabling psychiatric disorder that affects an estimated 51 million individuals worldwide (1,2). Psychosis, characterized by disorganized thought, delusions, and hallucinations, is a prominent feature of the disorder that necessitates clinical intervention in most cases. These positive symptoms are typically self-referential, often persecutory, and highly distressing and debilitating (3,4). The pathophysiology of schizophrenia is largely unknown (5), and the complexity of its symptoms has made it difficult to characterize the neurobiology of psychosis in a principled and theory-driven manner. Here, we apply a novel theoretically motivated systems neuroscience framework and a specific large-scale brain network model (6,7) to investigate dynamic functional circuits in schizophrenia and their relation to psychosis.

The science of large-scale brain networks offers a powerful paradigm for characterizing the neurobiology of psychiatric disorders (7,8). The goal of mapping the complex phenotypic features of schizophrenia onto individual brain areas is now widely considered implausible, and there is a growing consensus that these features arise from aberrations of cognitive systems (7,9,10). However, most extant studies have lacked a theoretical framework for examining how aberrancies in neurocognitive networks that are fundamental to human cognition contribute to core psychotic symptoms of schizophrenia. Our investigation of large-scale brain organization focuses on a triple-network model (Figure 1A), which postulates that aberrant functional organization of key frontoparietal-opercular neurocognitive networks may underlie psychosis in schizophrenia (7). This model highlights the role of three networks that play distinct roles in human cognition and, specifically, cognitive control over external stimuli and internal mental processes. In particular, the triple-network model posits a central role for the salience network (SN) in aberrant

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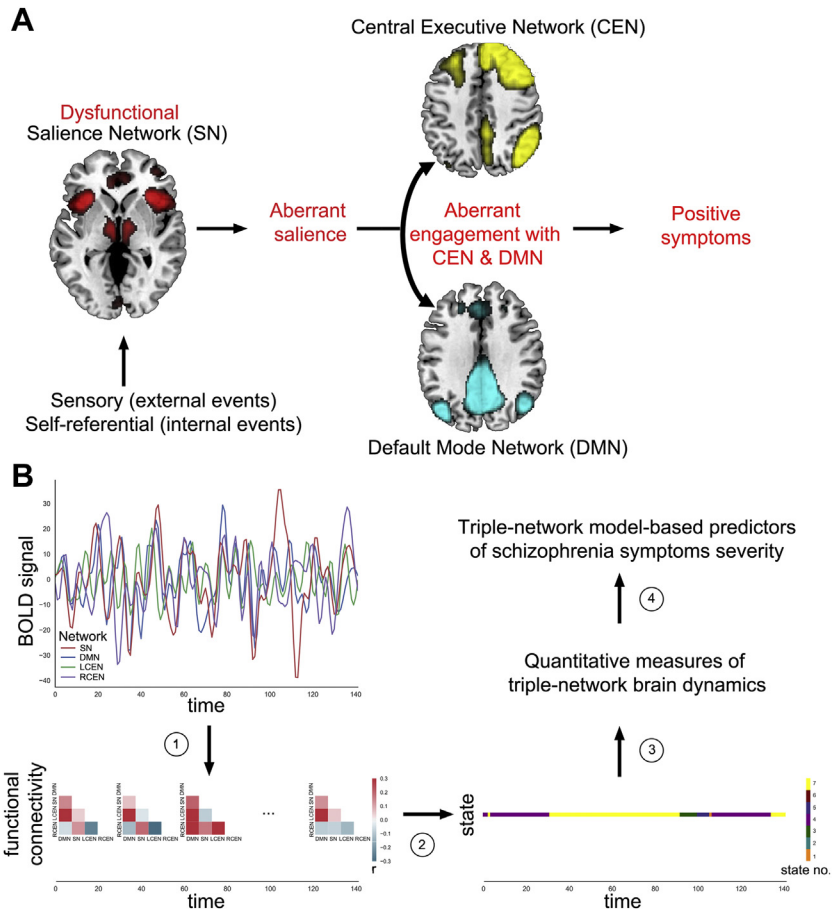

Figure 1. **(A)** Triple-network saliency model of schizophrenia. The model proposes that aberrant functional of organization of key frontoparietal-opercular cognitive networks may contribute to psychopathology in patients with schizophrenia. Specifically, this model posits a key role for the salience network (SN) in aberrant mapping of internal and external salient events, leading to altered dynamic temporal interactions with the central executive network (CEN), and the default mode network (DMN), resulting in clinical symptoms of psychosis. **(B)** Overall analysis pipeline for examining dynamic time-varying cross-network interactions within the triple-network saliency model. Time-varying cross-network interaction was measured using a dynamic functional connectivity approach. 1) We estimated dynamic functional interactions among the SN, CEN, and DMN using an exponentially decaying sliding window and a window length of 40 seconds (20 repetition times) and a sliding step of 2 seconds (1 repetition time). Exponentially decaying weights were applied to each time point within a window, as described in previous studies. Within each time window, we computed the *z*-transformed Pearson correlation between the independent component analysis time series taken pairwise. This resulted in a time series of correlation matrices (T×C); here, T is the number of time windows and C is number of pairwise interactions among the SN, CEN, and DMN at each time point. 2) To identify distinct group-specific states associated with dynamic functional connectivity, we applied groupwise *k*-means clustering on the time series of correlation matrices in each group separately. To quantify the dwelling time of dynamic brain states, we computed mean lifetime of each brain state for each participant, based on the average time spent continuously in that state. Two-sample *t* tests were conducted to evaluate the difference in mean lifetime between brain states in control and schizophrenia groups. 3) A brain state–specific network interaction index (NII) was used to characterize cross-network interaction in each dynamic brain state. The NII for each state *k* was computed by averaging NII across sliding-windows was labeled as state *k*. NII of a sliding window was computed as the difference in correlation between the SN and CEN time series and the correlation between the SN and DMN. The correlation values were extracted from the covariance matrix associated with that sliding window. The mean of the time-varying NII was calculated as the average of NII values across dynamics brain states; variability of time-varying NIIs was calculated as the standard deviation of NII values across dynamic brain states. 4) Canonical correlation analysis was used to examine the multivariate relation between dynamic time-varying cross-network interactions measures, including mean and variability of time-varying NIIs, and item-level Positive and Negative Syndrome Scale scores were used to measure positive or negative symptoms. BOLD, blood oxygen level–dependent; LCEN, left central executive network; RCEN, right central executive network.

mapping of external and internal salient events, leading to altered dynamic temporal interactions with the central executive network (CEN) and the default mode network (DMN). The SN, anchored in the anterior cingulate cortex and anterior insula, is crucial for salience mapping: detection of salient external stimuli and internal mental events and, through its interactions with the CEN and DMN, allocating attentional resources for additional processing (11–14). The CEN, anchored in the dorsolateral frontoparietal cortex, is involved in active maintenance and manipulation of information in working memory (11,15). In contrast, the DMN, anchored in the posterior cingulate cortex and ventromedial prefrontal cortex, is typically suppressed during focused attention to external stimuli and plays an important role in self-referential and autobiographical processes (11,16). Dynamic interactions among these three networks are essential for complex, goal-directed behaviors, and disturbances in these interactions may lead to aberrant mapping of external stimuli and internal mental processes and may contribute to positive symptoms observed in schizophrenia.

The SN is of particular interest here because of its central role in generating causal control signals that initiate dynamic switching between the CEN and DMN (11,15,17,18), thereby facilitating engagement of the CEN and disengagement of the DMN during cognitively demanding tasks (15). Recent research suggests that deficits in access, engagement, and disengagement of the SN, CEN, and DMN may underlie maladaptive behaviors and cognitive deficits (7,11,19,20). Although atypical patterns of intranetwork functional network organization have been variously reported in patients with schizophrenia (21), aberrancies in dynamic temporal interactions between these networks and their links to clinical symptoms in affected individuals remains unknown. Crucially, time-averaged or static connectivity provides limited information about the functional organization of brain circuits because interactions among

large-scale brain systems are highly nonstationary (22,23). Analysis of time-varying functional interactions among the SN, CEN, and DMN may therefore provide a more appropriate framework for investigating the psychopathology of schizophrenia (6,7). Building on our systems-level model of SN function, as well as our conceptualization of psychosis as aberrant detection, monitoring, and signaling of salient external stimuli and internal mental processes, we test the hypothesis that abnormalities in dynamic SN-centered functional interactions with the CEN and DMN may underlie psychosis in schizophrenia (6,7). Using data from two independent cohorts, we show that dynamic SN-centered cross-network functional interactions reliably distinguish patients with schizophrenia from healthy control subjects and predict positive symptoms in patients.

METHODS AND MATERIALS

Participants

Primary Cohort. Thirty-five patients with schizophrenia and 35 age-, sex-, and IQ-matched control subjects participated in this study after providing parental consent according to guidelines of the University of New Mexico Institutional Review Board. The patients with schizophrenia ranged from 18 to 62 years of age (mean age 34.4 years); the control subjects ranged from 18 to 65 years of age (mean age 36 years) (Table 1; see Supplement for details).

Replication Cohort. Thirty patients with schizophrenia and 30 age- and sex-matched control subjects participated in this study after providing informed consent according to the guidelines of the Hartford Hospital Institutional Review Board (24). The patients with schizophrenia ranged from 19 to 64 years of age (mean age 31.47 years); the control subjects ranged from 19 to 64 years of age (mean age 33.83 years) (Supplemental Table S1; see Supplement for details).

Table 1. Descriptive Statistics for the Schizophrenia and Control Groups

	Schizophrenia Group (n = 35)	Control Group (n = 35)	p Value
Age, Years	34.4 (12.6)	36.0 (12.2)	.58
Female/Male	5/30	11/24	.15
Handedness (Left/Both/Right)	5/0/30	0/0/35	.06
IQ	102 (14)	106 (15)	.25
PANSS Positive Symptoms Score	14.6 (4.3)	NA	NA
PANSS Negative Symptoms Score	15.2 (5.8)	NA	NA
Range of Head Motion			
X, mm	0.27 (0.22)	0.36 (0.29)	.15
Y, mm	0.59 (0.27)	0.56 (0.25)	.54
Z, mm	1.04 (0.63)	1.09 (0.62)	.74
Pitch, mm	0.82 (0.66)	0.93 (0.59)	.44
Roll, mm	0.30 (0.19)	0.37 (0.15)	.08
Yaw, mm	0.28 (0.19)	0.39 (0.34)	.13

Values are mean (SD) or n. The two groups were matched on age, sex, handedness, IQ, and head motion during functional magnetic resonance imaging. Two-sample t tests were used to compare age, IQ, and head motion parameters between the two groups, and χ^2 test was used to compare sex distribution and handedness.

NA, not applicable; PANSS, Positive and Negative Syndrome Scale.

Functional Magnetic Resonance Imaging

Each participant underwent a resting-state functional magnetic resonance imaging (fMRI) scan. The fMRI acquisition protocol is described in detail in the Supplement. Below we describe procedures used to analyze the primary cohort fMRI data. Identical procedures were used to analyze the replication cohort fMRI data.

Network Identification. Preprocessed resting-state fMRI data from the schizophrenia and control participants were concatenated and entered into a group independent component analysis to identify the SN, left CEN, right CEN, and DMN in the combined population (see Supplement for details).

Dynamic Time-Varying Cross-Network Interactions. Time-varying cross-network interaction was measured using a dynamic functional connectivity approach (25–27). Our overall analysis pipeline is illustrated in Figure 1B and described in detail in the Supplement. Briefly, we first estimated dynamic functional interactions among the SN, CEN, and DMN using an exponentially decaying sliding window. Second, we identified distinct group-specific states associated with dynamic functional connectivity using a groupwise k-means clustering approach. Third, we computed the mean lifetime of each brain state for each participant based on the average time spent continuously in that state. Fourth, we characterized cross-network interaction in each dynamic brain state using a brain state–specific network interaction index (NII). The NII measures cross-network interactions among the three networks based on the hypothesized role of the SN in switching interactions with the CEN and DMN (11,28). The NII has the advantage of capturing interactions simultaneously among all three networks. Specifically, the NII was computed as the difference in correlation between the SN and CEN time series and correlation between the SN and DMN. The NII thus captures the extent to which the SN temporally engages with the CEN and dissociates itself from the DMN (28,29). We computed an NII for each sliding window and averaged NIIs for the windows corresponding to the same dynamic brain state. We next computed the mean and variability (measured by standard deviation) of time-varying NIIs across all the dynamic brain states for each participant and examined the difference between the mean and variability of time-varying NIIs between the two groups.

Dynamic Time-Varying Cross-Network Interactions–Based Classification of Schizophrenia. To further investigate the robustness of differences in time-varying cross-network interactions, we examined whether the mean and variability of a dynamic time-varying NII could distinguish between the two groups in each cohort individually. To address the possibility of overfitting owing to the different number of clusters in the two groups, we also

investigated whether classifier trained from one cohort could be used to distinguish patients with schizophrenia from control subjects in the other cohort. Within- and cross-cohort classification procedures are described in detail in the Supplement.

Relation of Dynamic Time-Varying Cross-Network Interactions to Schizophrenia Symptoms. We used a Pearson correlation analysis and canonical correlation analysis (CCA) to examine the univariate and multivariate relation between the dynamic time-varying cross-network interaction measures, including the mean and variability of time-varying NIIs, and used item-level Positive and Negative Syndrome Scale scores to measure positive or negative symptoms. CCA is a statistical method for examining the relationships between two multivariate sets of variables and has been shown to be a powerful tool for investigating brain–behavior relationships (30,31). CCA finds an optimal linear combination of multivariate behavioral measures that maximize the relation between behavioral and brain measures.

RESULTS

Dynamic Time-Varying Cross-Network Interactions

We examined dynamic time-varying functional interactions among the four independent component analysis–identified brain networks (Supplemental Figure S1) and found seven states (temporal clusters) in the schizophrenia group and two in the control group (Figure 2A), reflecting variation in cross-network interactions across time in both groups.

Next, we compared mean lifetime of dynamic brain states between the two groups. The mean lifetime of state 1 in the control group was significantly longer than the mean lifetime of six of the seven states in the schizophrenia group (all p values $< .05$, false discovery rate corrected) (Figure 2B). The mean lifetime of state 2 in the control group was significantly longer than the mean lifetime of any of the seven states in the schizophrenia group (all p values $< .05$, false discovery rate corrected). These results demonstrate that compared with control subjects, individuals with schizophrenia show less persistent and more volatile brain states.

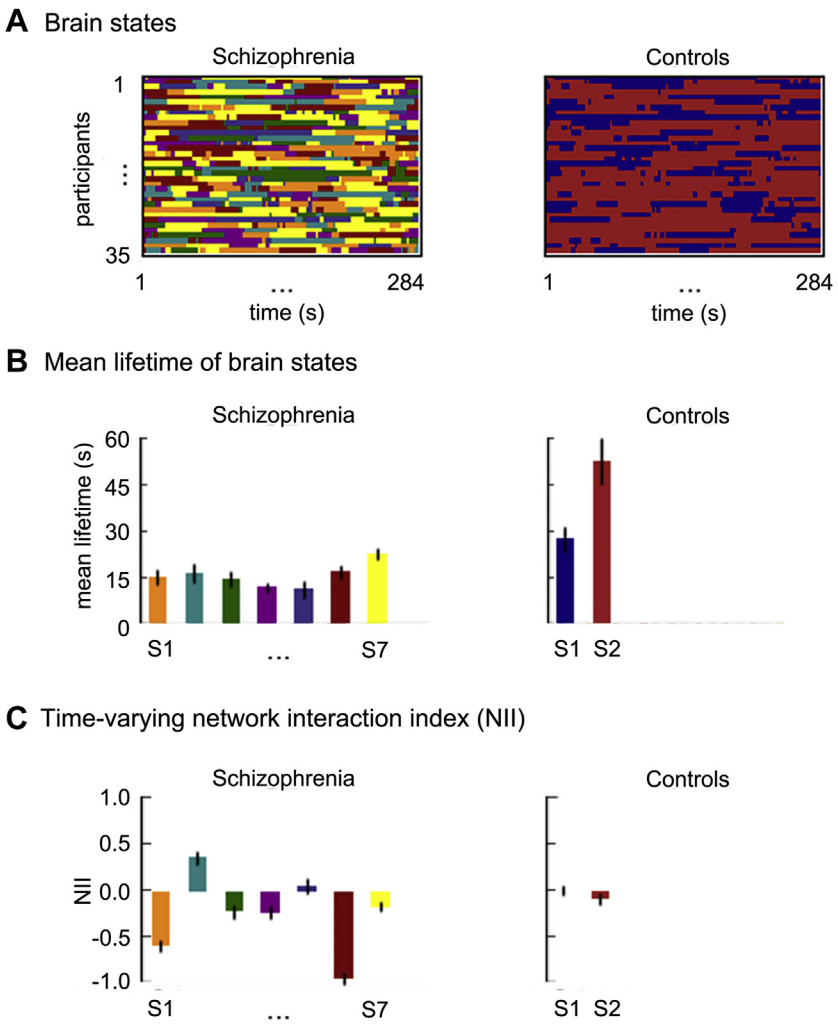

Figure 2. Dynamic time-varying cross-network interactions among the salience network, central executive network, and default mode network in the schizophrenia and control groups. **(A)** The schizophrenia group showed seven states (S1 to S7), significantly higher than the two states in the control group. Color codes show distinct states in each participant. **(B)** Mean lifetimes of dynamic brain states were shorter in the schizophrenia group compared with the control group. **(C)** The network interaction index (NII) of dynamic brain states shows intermittently reduced, and more variable, salience network–centered cross-network interaction in the schizophrenia group compared with the control group.

We then compared the NII of the dynamic brain states between the two groups. The mean NII value, averaged across all states, was significantly lower in the schizophrenia group compared with the control group ($p < .05$, Cohen's $d = 0.61$) (Figures 2C and 3A), even after controlling for confounds (Supplemental Table S5). These results demonstrate an intermittent lack of integration of the SN with the CEN and reduced decoupling of the SN from the DMN in schizophrenia.

We next compared variability of dynamic time-varying cross-network interactions between the two groups and found that compared with control subjects, individuals with schizophrenia showed greater variability in NII values across states, suggesting that cross-network interactions are more variable in the schizophrenia group than in the control group ($p < .0001$; Cohen's $d = 1.27$) (Figures 2C and 3A). Additional analyses further confirmed greater temporal variability of NII values in the schizophrenia group than in the control group after controlling for confounds (Supplemental Table S6).

The aforementioned results were also observed for a different sliding window length (50 seconds) as well as for a different sliding window shape (rectangular), demonstrating that the findings are robust against the length and shape of the sliding window (see Supplement for details).

Classification Based on Dynamic Time-Varying Cross-Network Interactions

We next examined whether SN-centered time-varying cross-network interactions could distinguish patients with schizophrenia from control subjects, using a classifier along with mean and variability of time-varying NII as features. SN-centered time-varying cross-network interaction patterns distinguished patients with schizophrenia from control subjects with a leave-one-out cross-validation accuracy of 78% ($p < .001$), sensitivity of 72%, and specificity of 83%.

Relationship Between Dynamic Time-Varying Cross-Network Interactions and Schizophrenia Symptoms

CCA revealed a significant relation between measures of SN-centered time-varying cross-network interactions and Positive and Negative Syndrome Scale scores used to measure positive symptoms ($p < .05$; Pillai's trace = 0.69). Specifically, CCA identified one significant pattern of interdependence between measures of time-varying interactions and positive symptoms assessed using the Positive and Negative Syndrome Scale ($p < .05$; $r = .67$). The conventional positive symptoms conceptual disorganization and hallucinatory behavior had a strong positive loading. Notably, the four

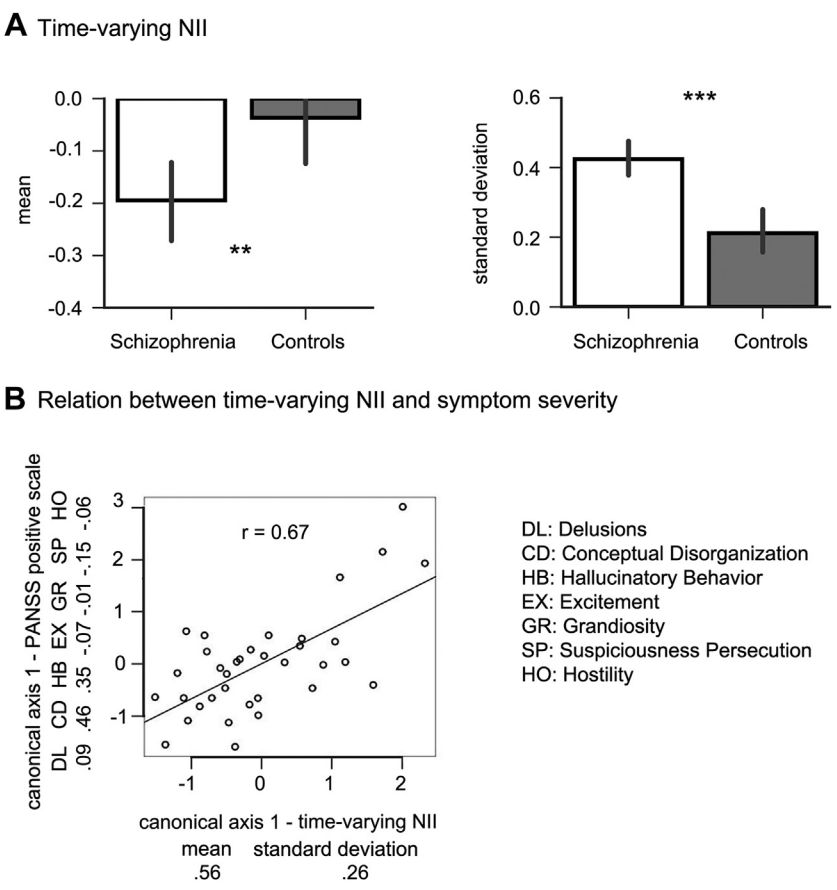

Figure 3. Mean and variability of dynamic cross-network interactions among the salience network, central executive network, and default mode network in the schizophrenia and control groups, and relation to positive symptoms. **(A)** The temporal mean of dynamic cross-network interactions, assessed using the mean of the dynamic network interaction indices (NIIs) across states, was significantly lower in the schizophrenia group compared with the control group. Additionally, the temporal variability of dynamic cross-network interaction, assessed using the standard deviation of the dynamic NIIs across states, was significantly higher in the schizophrenia group compared with the control group. $^{**}p < .01$; $^{***}p < .001$. **(B)** The temporal mean and variability of dynamic NIIs was strongly correlated with positive symptoms of schizophrenia, as revealed by canonical correlation analysis ($p < .05$; canonical correlation in first axis: $r = .67$). The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of symptoms.

nonspecific symptoms suspiciousness, excitement, grandiosity, and hostility had weak, close-to-zero loading (Figure 3B). The CCA model included both the mean and variability of dynamic time-varying cross-network interactions, explaining 44% of the variance. Neither measure individually predicted severity of positive symptoms (all p values $> .05$). Neither CCA nor individual measures of time-varying cross-network interactions predicted negative symptoms (all p values $> .05$).

To further examine the specificity of this brain–behavior correlation in patients with schizophrenia, we examined the relationship between dynamic time-varying cross-network interactions and cognitive abilities. Neither CCA-based latent variables nor individual measures of time-varying cross-network interactions predicted cognitive abilities, as measured by Measurement and Treatment Research to Improve Cognition Schizophrenia (MATRICS) scores (all p values $> .05$).

Dynamic Time-Varying Cross-Network Interactions Versus Static Time-Averaged Cross-Network Interactions

To demonstrate the specificity of our dynamic cross-network interaction findings, we examined static time-averaged interactions among the SN, CEN, and DMN (see Supplement for details). The time-averaged SN-centered NII was significantly lower in the schizophrenia group than in the control group ($p < .05$) (Supplemental Figure S2), albeit with an effect size (Cohen's $d = 0.60$) lower than that observed for variability in dynamic cross-network interactions.

We next evaluated time-averaged cross-network interactions for their ability to distinguish patients with schizophrenia from control subjects, using a classifier. Time-averaged cross-network interaction patterns distinguished patients with schizophrenia from control subjects with an accuracy that was not significantly different from the chance level (leave-one-out cross-validation accuracy = 50%, sensitivity = 53%, specificity = 47%) and much lower than the values observed for dynamic cross-network interactions based classification (see Supplement for details).

Last, we examined the relationship between time-averaged cross-network interactions and schizophrenia symptoms or cognitive abilities. Unlike measures of dynamic cross-network interactions, we found no significant multivariate relation between measures of time-averaged cross-network and item-level positive symptoms (see Supplement for details).

Reproducibility of Findings

In recent years, there has been increasing concern about reproducibility of neuroscientific findings (32). To address this concern and to determine the replicability of our findings, we examined dynamic time-varying cross-network interactions among the SN, CEN, and DMN in patients with schizophrenia versus control subjects in an independent cohort (replication cohort). Results were consistent with those observed in the primary cohort: 1) dynamic SN-centered cross-network interactions were significantly reduced, less persistent, and more variable in patients with schizophrenia compared with control subjects; 2) multivariate classification analysis corroborated identified dynamic SN-centered cross-network interaction patterns as factors that distinguish patients from control subjects, with an accuracy of 80%, sensitivity of 87%, and specificity of 73%; 3) dynamic time-varying measures of SN-centered cross-network interactions were correlated with positive symptoms but not with negative symptoms; and 4) time-averaged SN-centered cross-network interactions were not significantly between the two groups. Detailed findings from the replication cohort are in the Supplement.

To further evaluate the generalizability of our findings, we used task-free fMRI data from the Human Connectome Project (33) and compared the dynamics in this normative control dataset against the schizophrenia group reported for the primary and the replication cohorts. Here again, we found that in both cohorts individuals with schizophrenia showed greater variability in dynamic SN-centered cross-network interactions than the Human Connectome Project normative control subjects did (see Supplement for details).

DISCUSSION

We investigated a triple-network model of aberrant salience mapping in schizophrenia focusing on dynamic functional interactions among the SN, CEN, and DMN, three large-scale brain networks important for cognitive control and goal-directed behavior. Consistent with our hypothesis, we found that the dynamic SN-centered functional interactions were aberrant in patients with schizophrenia. Notably, patients with schizophrenia showed significantly reduced and more volatile SN-centered cross-network interactions. Further, dynamic, but not time-averaged, cross-network coupling measures could distinguish patients from control subjects and predict psychosis symptoms in patients. Neither dynamic nor static connectivity measures associated with these networks predicted negative symptoms or cognitive abilities in the same group of patients. Our findings suggest that dynamic functional interactions of the SN with the CEN and DMN are impaired in schizophrenia and that these aberrations contribute to psychosis. Notably, our findings were replicated across two different cohorts and data acquired across different MRI scanners and sites.

Aberrant SN-Centered Cross-Triple-Network Coupling in Schizophrenia

Dynamic connectivity measures associated with the SN, CEN, and DMN differed between the groups in both cohorts. In contrast, static connectivity measures were different between the two groups only in one cohort, and with an effect size smaller than in the dynamic connectivity measures. Although considerable evidence for aberrant intrinsic functional connectivity in schizophrenia has emerged in recent years, most studies have focused on static measures of brain connectivity, and a range of findings ranging from hypo- and hyperconnectivity as well as normal connectivity between cortical areas has been reported (16,34–40). Critically, these studies have assumed that network interactions are stationary, and thus there have been few investigations of dynamic functional circuits and their relation to clinical symptoms in patients with schizophrenia.

SN-centered NII measures of dynamic cross-network interactions were significantly lower and more variable in the

schizophrenia group than in the control group in both cohorts. These effects were specific to SN interactions, as alternative models involving parallel constructs with CEN-centered and DMN-centered networks showed no differences between the groups. These findings demonstrate that reduced interaction of the SN with the CEN and DMN is a prominent feature of network level disorganization in schizophrenia and likely reflects difficulties in simultaneously disengaging the DMN and engaging the CEN (35,39). Given the central role for the SN in detection of salient stimuli and orienting attention to them, we suggest that dysfunction in cross-network interactions may contribute to impaired ability of patients to flexibly and dynamically allocate cognitively relevant processing resources (7,11,15,17,41,42).

Dynamic Brain States Linking the SN, CEN, and DMN Are More Volatile in Patients With Schizophrenia Than in Control Subjects

Our analysis of dynamic connectivity further revealed that interactions among the SN, CEN and DMN were less persistent and short lived. Moreover, our results point to an intermittent lack of integration of the SN with the CEN and decoupling of the SN from the DMN in schizophrenia. This pattern underlies the more variable and reduced SN-centered dynamic interactions with the CEN and DMN that we detected in the patient group. Crucially, our findings also demonstrate that such time-varying properties of functional interactions among the three networks provide a better framework for investigating the underlying pathophysiology of schizophrenia because they capture the dynamic engagement as well as the disengagement of relevant brain circuits.

SN-Centered Dynamic Connectivity Measures Distinguish Patients With Schizophrenia From Control Subjects

To determine the robustness of our findings, we used a machine learning approach to examine the extent to which dynamic and static measures associated with SN connectivity were distinct in patients versus control subjects. We found that SN-centered dynamic cross-network interactions distinguished patients from control subjects with high classification accuracy within each cohort as well as across the two cohorts. Furthermore, when compared with CEN- and DMN-centered NII measures, SN-centered dynamic cross-network interactions showed the highest discrimination rates between patients and control subjects in both cohorts, separately as well as across the two cohorts (see Supplement for details). Again, these findings were specific to dynamic NII measures, as static measures resulted in classification accuracies that were not significantly different from the chance level in both cohorts. Previous classification studies of patients with schizophrenia using static, time-averaged, intrinsic functional interaction patterns as features have reported accuracies better than chance level (43). This discrepancy could be attributed to the large number of features and relatively small number of participants used in these previous studies, which can cause overfitting and elevated, but biased, classification accuracies. Furthermore, there is no neurobiological model to interpret findings based on such a large number of brain-wide features. Our approach overcomes these limitations and demonstrates high cross-cohort classification rates using theoretically informed features from cognitive control systems.

Our findings suggest that aberrant SN-centered connectivity with the CEN and DMN is a robust distinguishing feature of schizophrenia. While the goal of the present work was not to develop predictive biomarkers of schizophrenia, our findings suggest that incorporating dynamic connectivity measures associated with the SN will be an important direction for future work that seeks to develop robust, clinically meaningful biomarkers of schizophrenia (44). Critically, in the context of the present study, our classification analysis of SN-related features provides evidence for aberrant functional brain organization in schizophrenia within the triple-network model.

Aberrant SN-Centered Dynamic, but Not Static, Network Interactions Predict Positive, but Not Negative, Symptoms or Cognitive Abilities

Within the SN-centered network model examined here, CCA revealed a distinct pattern of association between dynamic brain connectivity and severity of positive symptoms in patients. In particular, this pattern captures a positive association between lack of dynamic engagement of the SN with the CEN and DMN, and disorganized thoughts—that is, patients with the least persistent and most volatile time-varying SN-centered cross-network interactions exhibited the most severe conceptual disorganization, in both cohorts. Again, these effects were specific to dynamic SN-centered connectivity measures but not CEN- and DMN-centered measures. Further, consistent with other findings reported above, these effects were observed for dynamic, but not static, connectivity measures. Critically, no significant relationship was observed between SN-centered dynamic connectivity and negative symptoms or cognitive abilities. Thus, our dynamic internetwork connectivity measures allowed us to capture a crucial link to psychosis in ways that previous studies could not (7,20,35,45–48). We and others have previously reported that variations in the morphology, metabolism, and neural activity of the SN nodes are specifically related to positive symptoms (49), especially disorganized behavior that was observed in both cohorts (50–52). These results are consistent with our hypothesis that abnormal attribution of salience to external and internal stimuli is a core feature of schizophrenia and may explain the genesis of psychotic symptoms (6). Given that patients with very severe negative symptoms and cognitive dysfunction are often not available for neuroimaging studies, the possibility of insufficient power to demonstrate an association with the severity of these symptom domains cannot be ruled out. Furthermore, such associations may depend on inclusion of other cortical and subcortical structures, and other large-scale brain networks that were not considered here and transdiagnostic approaches with larger samples could capture the depth of variability in cognitive abilities in relation to SN dysfunction

(19,53). In either case, our findings suggest that links to cognitive deficits may be secondary to psychosis.

Our findings provide further evidence in support for the aberrant salience model (6) of psychosis and identify aberrant dynamic interactions of the SN as a major factor that contributes to this core symptom of schizophrenia. Although Kapur's original aberrant salience model is largely based on midbrain dopaminergic signaling of reward-based salience, recent extensions of the model have highlighted the role of aberrant cognitive control systems in the formation of delusions (6). Specifically, it has been suggested that any event, such as an external stimulus or an internal mental event, becomes salient when it generates transient neural activity within the SN that is large enough to trigger changes in other brain systems (6,46). In particular, switching mechanisms between CEN and DMN mediated by the SN (15) are likely to be crucial for appropriate allocation of attentional and working memory resources (6). Attributing salience to external stimuli and internal mental events whose processing places competing demands on the SN and its internetwork interactions may thus underlie the physiological basis underlying psychosis. Aberrations in SN circuit dynamics may lead to impaired weighting of saliency and perceptual priors, processes that have now been hypothesized to underlie hallucinations and disorganized thought (54,55). Furthermore, abnormalities in monitoring internal and external salient events extend beyond attentional capture and can also hinder adaptive updating of beliefs and knowledge in response to communicative cues (56). Consistent with this view, aberrant activity in the insula during ambiguous sentence processing has been previously reported in patients with psychosis (57). Taken together, these findings provide novel evidence that aberrations in the SN and the resulting impairments in salience attribution may contribute to psychosis.

Conclusions

Our study demonstrates that dynamic, but not static, time-varying measures of cross-network interactions among the SN, CEN, and DMN are a prominent and robust feature of schizophrenia. We identify dynamic cross-network interactions anchored on the SN as a locus of aberrant connectivity that distinguishes patients from control subjects and predicts individual differences in psychosis but not negative symptoms. Dynamic variations in SN-centered connectivity may provide a useful framework for differential characterization of positive symptoms in the disorder. Our findings, replicated across the two independent cohorts, provide novel support for a triple-network model of schizophrenia and provide a template for advancing future research on the neurobiological mechanisms and biomarkers of psychosis. Further studies are needed to examine the longitudinal stability of aberrant SN circuit dynamics during different stages of illness and to identify whether differences in clinical outcomes map on to varying levels of SN dysfunction. The effects of sex, exposure to medications, and long-term treatment on SN and triple-network model circuit dysfunction also warrant investigation. An important challenge for future work is to develop treatments that target SN dysfunction to ameliorate the debilitating effects of psychosis.

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REFERENCES

1. Saha S, Chant D, Welham J, McGrath J (2005): A systematic review of the prevalence of schizophrenia. PLoS Med 2:e141.
2. Shivashankar S, Telfer S, Arunagiriraj J, McKinnon M, Jauhar S, Krishnadas R, *et al.* (2013): Has the prevalence, clinical presentation and social functioning of schizophrenia changed over the last 25 years? Nithsdale schizophrenia survey revisited. Schizophr Res 146:349–356.
3. American Psychiatric Association (1994): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.
4. Oyebode F (2008): Sims' Symptoms in the Mind: An Introduction to Descriptive Psychopathology, 4th ed. Edinburgh, UK: W.B. Saunders.
5. Insel TR (2010): Rethinking schizophrenia. Nature 468:187–193.
6. Palaniyappan L, Liddle PF (2012): Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J Psychiatry Neurosci 37:17–27.

7. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 15:483–506.
8. Dong D, Wang Y, Chang X, Luo C, Yao D (2017): Dysfunction of large-scale brain networks in schizophrenia: A meta-analysis of resting-state functional connectivity. Schizophr Bull 44:161–181.
9. Fornito A, Bullmore ET (2014): Connectomics: A new paradigm for understanding brain disease. Eur Neuropsychopharmacol 25:733–748.
10. Meyer-Lindenberg A (2010): From maps to mechanisms through neuroimaging of schizophrenia. Nature 468:194–202.
11. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. Brain Struct Funct 214:655–667.
12. Chen T, Michels L, Supekar K, Kochalka J, Ryali S, Menon V (2015): Role of the anterior insular cortex in integrative causal signaling during multisensory auditory-visual attention. Eur J Neurosci 41:264–274.
13. Cai W, Chen T, Ryali S, Kochalka J, Li CS, Menon V (2016): Causal interactions within a frontal-cingulate-parietal network during cognitive control: Convergent evidence from a multisite-multitask investigation. Cereb Cortex 26:2140–2153.
14. Cai W, Chen T, Ide JS, Li CR, Menon V (2017): Dissociable fronto-operculum-insula control signals for anticipation and detection of inhibitory sensory cue. Cereb Cortex 27:4073–4082.
15. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A 105:12569–12574.
16. Whitfield-Gabrieli S, Ford JM (2012): Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 8:49–76.
17. Ham T, Leff A, de Boissezon X, Joffe A, Sharp DJ (2013): Cognitive control and the salience network: An investigation of error processing and effective connectivity. J Neurosci 33:7091–7098.
18. Supekar K, Menon V (2012): Developmental maturation of dynamic causal control signals in higher-order cognition: A neurocognitive network model. PLoS Comput Biol 8:e1002374.
19. Sheffield JM, Kandala S, Tamminga CA, Pearlson GD, Keshavan MS, Sweeney JA, *et al.* (2017): Transdiagnostic associations between functional brain network integrity and cognition. JAMA Psychiatry 74:605–613.
20. Baker JT, Holmes AJ, Masters GA, Yeo BT, Krienen F, Buckner RL, *et al.* (2014): Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. JAMA Psychiatry 71:109–118.
21. Wang X, Zhang W, Sun Y, Hu M, Chen A (2016): Aberrant intra-salience network dynamic functional connectivity impairs large-scale network interactions in schizophrenia. Neuropsychologia 93:262–270.
22. Chen T, Cai W, Ryali S, Supekar K, Menon V (2016): Distinct global brain dynamics and spatiotemporal organization of the salience network. PLoS Biol 14:e1002469.
23. Calhoun VD, Miller R, Pearlson G, Adali T (2014): The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84:262–274.
24. Tamminga CA, Ivleva EI, Keshavan MS, Pearlson GD, Clementz BA, Witte B, *et al.* (2013): Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 170:1263–1274.
25. Cai W, Chen T, Szegletes L, Supekar K, Menon V (2018): Aberrant time-varying cross-network interactions in children with attention-deficit/hyperactivity disorder and the relation to attention deficits. Biol Psychiatry Cogn Neurosci Neuroimaging 3:263–273.
26. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M (2014): Time-resolved resting-state brain networks. Proc Natl Acad Sci U S A 111:10341–10346.
27. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD (2014): Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex 24:663–676.
28. Menon V (2015): Large-scale functional brain organization. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. New York: Elsevier, 449–459.
29. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100:253–258.
30. Smith SM, Nichols TE, Vidaurre D, Winkler AM, Behrens TE, Glasser MF, *et al.* (2015): A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nat Neurosci 18:1565–1567.
31. Perry A, Wen W, Kochan NA, Thalamuthu A, Sachdev PS, Breakspear M (2017): The independent influences of age and education on functional brain networks and cognition in healthy older adults. Hum Brain Mapp 38:5094–5114.
32. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, *et al.* (2013): Power failure: Why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 14:365–376.
33. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, *et al.* (2013): The WU-Minn Human Connectome Project: An overview. Neuroimage 80:62–79.
34. Karbasforoushan H, Woodward ND (2012): Resting-state networks in schizophrenia. Curr Top Med Chem 12:2404–2414.
35. Manoliu A, Riedl V, Zherdin A, Muhlau M, Schwerthoffer D, Scherr M, *et al.* (2013): Aberrant dependence of default moede/central executive network interactions on anterior insular salience network activity in schizophrenia. Schizophr Bull 40:428–437.
36. Orliac F, Naveau M, Joliot M, Delcroix N, Razafimandimby A, Brazo P, *et al.* (2013): Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. Schizophr Res 148:74–80.
37. Woodward ND, Rogers B, Heckers S (2011): Functional resting-state networks are differentially affected in schizophrenia. Schizophr Res 130:86–93.
38. Lui S, Li T, Deng W, Jiang L, Wu Q, Tang H, *et al.* (2010): Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. Arch Gen Psychiatry 67:783–792.
39. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD (2008): A method for functional network connectivity among spatially independent resting-state components in schizophrenia. Neuroimage 39:1666–1681.
40. Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A (2011): Dysconnectivity in schizophrenia: Where are we now? Neurosci Biobehav Rev 35:1110–1124.
41. Menon V (2013): Developmental pathways to functional brain networks: Emerging principles. Trends Cogn Sci 17:627–640.
42. Bonnelle V, Ham TE, Leech R, Kinnunen KM, Mehta MA, Greenwood RJ, *et al.* (2012): Salience network integrity predicts default mode network function after traumatic brain injury. Proc Natl Acad Sci U S A 109:4690–4695.
43. Arbabshirani MR, Plis S, Sui J, Calhoun VD (2017): Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. Neuroimage 145:137–165.
44. Palaniyappan L, Deshpande G, Lanka P, Rangaprakash D, Iwabuchi S, Francis S, Liddle PF (2018): Effective connectivity within a triple network brain system discriminates schizophrenia spectrum disorders from psychotic bipolar disorder at the single-subject level [published online ahead of print Feb 2]. Schizophr Res.
45. Moran LV, Tagamets MA, Sampath H, O'Donnell A, Stein EA, Kochunov P, *et al.* (2013): Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. Biol Psychiatry 74:467–474.
46. Palaniyappan L, Simmonite M, White TP, Liddle EB, Liddle PF (2013): Neural primacy of the salience processing system in schizophrenia. Neuron 79:814–828.
47. Penner J, Ford KA, Taylor R, Schaefer B, Theberge J, Neufeld RW, *et al.* (2016): Medial prefrontal and anterior insular connectivity in early schizophrenia and major depressive disorder: A resting functional MRI

evaluation of large-scale brain network models. Front Hum Neurosci 10:132.
48. White TP, Gilleen J, Shergill SS (2013): Dysregulated but not decreased salience network activity in schizophrenia. Front Hum Neurosci 7:65.
49. Walter A, Suenderhauf C, Smieskova R, Lenz C, Harrisberger F, Schmidt A, *et al.* (2016): Altered insular function during aberrant salience processing in relation to the severity of psychotic symptoms. Front Psychiatry 7:189.
50. Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Carpenter WT, McMahon R (2006): Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. Neuropsychopharmacology 31:221–230.
51. Horn H, Federspiel A, Wirth M, Muller TJ, Wiest R, Wang JJ, *et al.* (2009): Structural and metabolic changes in language areas linked to formal thought disorder. Br J Psychiatry 194:130–138.
52. Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RS (1992): Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160:179–186.
53. Sheffield JM, Barch DM (2016): Cognition and resting-state functional connectivity in schizophrenia. Neurosci Biobehav Rev 61:108–120.
54. Powers AR, Mathys C, Corlett PR (2017): Pavlovian conditioning-induced hallucinations result from overweighting of perceptual priors. Science 357:596–600.
55. Powers AR 3rd, Kelley M, Corlett PR (2016): Hallucinations as top-down effects on perception. Biol Psychiatry Cogn Neurosci Neuroimaging 1:393–400.
56. Sitnikova T, Goff D, Kuperberg GR (2009): Neurocognitive abnormalities during comprehension of real-world goal-directed behaviors in schizophrenia. J Abnorm Psychol 118:256–277.
57. Menon M, Schmitz TW, Anderson AK, Graff A, Korostil M, Mamo D, *et al.* (2011): Exploring the neural correlates of delusions of reference. Biol Psychiatry 70:1127–1133.