Aberrant Dependence of Default Mode/Central Executive Network Interactions on Anterior Insular Salience Network Activity in Schizophrenia

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In schizophrenia, consistent structural and functional changes have been demonstrated for the insula including aberrant salience processing, which is critical for psychosis. Interactions within and across default mode and central executive network (DMN, CEN) are impaired in schizophrenia. The question arises whether these 2 types of changes are related. Recently, the anterior insula has been demonstrated to control DMN/CEN interactions. We hypothesized that aberrant insula and DMN/CEN activity in schizophrenia is associated with an impaired dependence of DMN/CEN interactions on anterior insular salience network (SN) activity. Eighteen patients with schizophrenia during psychosis and 20 healthy controls were studied by resting-state-fMRI and psychometric examination. High-model-order independent component analysis of fMRI data revealed spatiotemporal patterns of synchronized ongoing blood-oxygenation-level-dependent (BOLD) activity including SN, DMN, and CEN. Scores of functional and time-lagged connectivity across networks' time courses were calculated. Connectivity scores and spatial network maps were compared between groups and related with patients' hallucination and delusion severity. Spatial BOLD-synchronicity was altered in patients' SN, DMN, and CEN, including decreased activity in the right anterior insula (rAI). Patients' functional connectivity between DMN and CEN was increased and related with hallucinations severity. Importantly, patients' time-lagged connectivity between SN and DMN/CEN was reduced, and decreased rAI activity of the SN was associated with both hallucinations and increased functional connectivity between DMN and CEN. Data provide evidence for an aberrant dependence of DMN/CEN interactions on anterior insular SN activity, linking impaired insula, DMN, CEN activity, and psychosis in schizophrenia.

Key words: schizophrenia/psychosis/anterior insula/salience network/default mode network/central executive network

Introduction

The insula is consistently changed in schizophrenia.[1] Patients with schizophrenia are characterized by insula gray matter decreases,[2] reduced white matter fractional anisotropy,[3] and altered functional activity for various tasks.[4] The insula is part of the salience network (SN), further comprising fronto-insular operculum and dorsal anterior cingulate cortex (dACC).[5] The SN is an intrinsic connectivity network (ICN), characterized by spatially consistent functional connectivity (FC) of intrinsic brain activity.[6] Salience network and insula are involved in the detection and processing of emotionally salient events.[5] Particularly, the insula supports representations and updating of current and predictive salience,[1,7] especially in the context of interoception.[8] Theoretical models and experimental data suggest that altered salience and salience prediction error coding may underlie psychotic symptoms.[1,4,9,10] In particular, it has been suggested that the assignment of aberrant "proximal salience" to internally generated mental events (such as inner speech or self-generated actions) contributes to impaired self-monitoring, which explains hallucinations or passivity experiences within a Bayesian framework of positive symptoms.[1,10]

Beyond insula and SN, the default mode and central executive networks (DMN, CEN) are further ICNs consistently altered in schizophrenia.[11] The DMN is involved in self-related/internally oriented processes, the CEN in goal-directed/externally oriented tasks.[6] Schizophrenia is associated with disrupted task-state activity[11–13] and resting-state activity[12,14,15] of these 2 networks including altered interactions among networks.[16] It has been suggested that aberrant interactions of anticorrelated DMN and CEN represent a core feature of schizophrenia, underlying patients' impaired coordination of self-monitoring and task-performance.[17]

Based on these findings, the question arises how insular and DMN/CEN changes are related in schizophrenia. Recently, it has been demonstrated that the insular SN controls interactions between DMN and CEN (ie in terms of task-processing: switches between self-related and external-task-directed processes depend on salience processing).[18,19] We hypothesized for schizophrenia that aberrant insula and DMN/CEN activity in psychosis is associated with an impaired dependence of DMN/CEN interactions on anterior insular SN activity. This suggestion corresponds with recent, independently formulated models of aberrant insula function in schizophrenia.[1,20]

To test this hypothesis, we used resting-state (rs)-fMRI, measuring ongoing blood-oxygenation-level-dependent (BOLD) fluctuations, in patients with schizophrenia during psychosis and healthy controls. Resting-state activity is used as a surrogate for intrinsic brain activity, which is organized by temporal relationships among regions; rs-fMRI facilitates to detect patterns of coherent intrinsic activity underlying ICNs.[6] To identify SN, DMN and CEN, rs-fMRI data were decomposed by high-model-order independent component analysis (ICA) into spatially independent z-maps and corresponding time courses (TCs) of component activity.[21] Component z-maps reflect brain areas of distinctive FC of resting-state activity, which characterize ICNs (intra-iFC). Pearson's correlation and time-lagged correlation between components time series (inter-iFC, lagged inter-iFC) were the study's main outcome measures, reflecting FC and temporal dependencies between ICNs.

Methods

Participants

Eighteen patients and 20 healthy controls participated in the study (table 1). They provided informed consent in accordance with the Human Research Committee guidelines of the Klinikum Rechts der Isar, Technische Universität München. Patients were recruited from the Department of Psychiatry, controls by word-of-mouth advertising. Participants' examination included medical history, psychiatric interview, psychometric assessment, and blood tests for patients. Psychiatric diagnoses were based on DSM IV.[22] The Structured Clinical Interview for

Table 1. Demographic and Clinical Characteristics

Measure	SA (n = 18) Mean (SD)	HC (n = 20) Mean (SD)	SA vs HC[a] T Score	P Value
Age	35.33 (12.49)	34.00 (13.35)	0.317	.753
Sex (m/f)	9/9	9/11		
PANSS				
Total	76.44 (18.45)	30.15 (0.67)	11.231	<.001*
Positive	18.06 (5.74)	7.05 (0.22)	8.574	<.001*
Negative	19.94 (8.11)	7.10 (0.45)	7.08	<.001*
General	37.67 (9.93)	16.05 (0.23)	9.743	<.001*
GAF	41.50 (11.55)	99.75 (1.12)	−22.478	<.001*
CPZ	466.72 (440.49)			

Note: SA, patients with schizophrenia during acute state of psychosis; HC, healthy control group; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning Scale; CPZ, chlorpromazine equivalent dose.
[a]2-sample t test.
*significant for P < .05, Bonferroni-corrected for multiple comparisons.

DSM-IV (SCID-I)[23] was used to assess the presence of psychiatric diagnoses. Severity of clinical symptoms was measured with the Positive and Negative Syndrome Scale (PANSS)[24] on the day of scanning. Psychiatrists D.S. and M.S., who performed clinical-psychometric assessment, have been professionally trained for SCID and PANSS-based interviews with inter-rater reliability for diagnoses and scores of more than 95%. The global level of social, occupational, and psychological functioning was measured with the Global Assessment of Functioning Scale (GAF).[23]

All patients were diagnosed with schizophrenia and were in-patient at the time-point of scanning. Further inclusion criteria were age between 18 and 60 years and current psychotic symptoms. Patients were free of any current or past neurological or internal systemic disorder, current or past depressive or manic episode, substance abuse (except nicotine) and cerebral pathology in MRI. The mean duration of illness was 7.00 years (SD = 6.84 years), the mean number of hospital stays was 2,92 (SD = 2,43). Two out of 18 patients were free of antipsychotic medication. All other patients received mono- or dual therapy with atypical antipsychotic medication, including Amilsupride (n = 1 case), Olanzapine (n = 11), Clozapine (n = 4), Quetiapine (n = 3), Ziprasidone (n = 1), Risperidone (n = 4), Aripiprazole (n = 2) and Paliperidone (n = 3) (supplementary table S1 for individual medication protocols and dosage; table 1 for mean chlorpromazine [CPZ] equivalent dose).[25] All controls were free of any current or past psychiatric, neurological or systemic disorder or psychotropic medication.

All participants underwent 10 min of rs-fMRI with the instruction to keep their eyes closed and not to fall asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan. Before

and after scanning, a medical examination of patients validated their stable condition and investigated whether they had feelings of odd situations during the scanning. No patient dropped out during the scanning session.

FMRI Data Analysis

Detailed descriptions of the MRI data acquisition parameters, data preprocessing, and procedures of data quality check was presented previously[26] and in the online supplementary material.

ICA and Selection of Networks-of-Interest. The selection of the optimal ICA model-order to analyze rs-fMRI data is still a subject of ongoing debate. However, it has been demonstrated that a model-order around 70 components may represent an optimal level to detect between-group differences and to avoid false positive results.[27,28] Bearing this in mind and exactly following a recently proposed approach of,[28] we decomposed our data into 75 independent components. The correspondence with Allen's approach enables greater comparability of results across studies and reduced subjective bias for ICN selection. In more detail, Allen and colleagues used an ICA model-order of 75 to decompose rs-fMRI data of 603 subjects within a group-ICA framework based on the infomax-algorithm and implemented in the GIFT-software (http://icatb.sourceforge.net)[21] (see the online supplementary material). Authors provided online T-maps of 28 components, which reflect canonical ICNs.[28] To select components, which reflect networks-of-interest, in an automated and objective way, we chose from these T-maps those of SN, DMN, and CEN (7 of 28 maps, see online supplementary material), and performed multiple spatial regression analyses of our 75 independent components' spatial maps on these templates. We selected components of highest correlation coefficient with the templates, resulting in 7 ICNs of interest: 1 component reflecting the SN, 3 reflecting subsystems of the DMN or CEN, respectively. In the end, this approach yielded for each subject and ICN a component's z-map and TC, which reflect network's coherent activity.

Outcome Measures Intra-iFC, Inter-iFC, and Lagged Inter-iFC. From ICNs' z-maps and TCs, we derived main outcome measures as described previously[26,29] and in the online supplementary material. Basically, z-maps reflect intra-iFC of an ICN. Inter-iFC between 2 ICNs is defined by Pearson's correlation of corresponding TCs. Lagged inter-iFC of the SN onto DMN- or CEN-subsystems (reflecting the temporal dependence of these subsystems activity from SN activity) relies basically on the correlation between SN's TC and time-lag-shifted TCs of DMN/CEN-subsystems. To study the relationship among these outcome measures and PANSS scores for hallucination and delusion in patients, we performed corresponding partial correlation analyses, which included age, sex,

CPZ, and total gray matter (GM) volume as covariates-of-no-interest. GM volumes were derived from a voxel-based-morphometry analysis described previously[26] and in the online supplementary material.

Results

Group Comparisons for PANSS Scores and Brain Structure

Patients had significantly increased PANSS scores for items hallucinations, delusion, total positive symptoms, and total score (table 1). Total GM did not differ significantly across groups, although patients showed minor decreases ($T = -0.95$, $P = .35$). Furthermore, voxel-wise tests yielded no regional GM or white matter changes.

Intrinsic Connectivity Networks: Intra- and Inter-iFC

Selected components representing ICNs-of-interest were spatially consistent across groups and matched previous results of SN, DMN, and CEN[28,30,31] (figure 1 and table S2; $P < .05$ FWE-corrected; detailed description in the online supplementary material). Inter-iFC between intrinsic networks is presented in figure 2 and table 2 and matched almost perfectly results of Allen and colleagues[28] (detailed description in the online supplementary material). Noteworthy, the direction of the inter-network connectivity correlation coefficients was in all but one case the same for both groups.

Intra-iFC of the SN Is Disrupted in Bilateral Anterior Insula in Psychotic Patients

Compared with healthy controls, patients showed altered intra-iFC within the SN, DMN, and CEN (figure 1 and table S3; $P < .05$ FWE-corrected). Regarding the SN, patients showed both decreased intra-iFC in bilateral AI and increased iFC in bilateral ACC (figure 1D). Regarding the DMN, patients showed decreased intra-iFC in bilateral ACC (figure 1A) and bilateral precuneus (figure 1B,C). Regarding the CEN, patients showed decreased intra-iFC in bilateral inferior parietal lobule and bilateral frontal gyrus and increased intra-iFC in the right angular gyrus and left inferior temporal gyrus (figure 1E–G).

Inter-iFC Between DMN and CEN Is Increased in Psychotic Patients

Compared with healthy controls, psychotic patients showed increased inter-iFC (figure 2, figure 3, table 2; $P < .05$, Bonferroni-corrected). Patients showed increased inter-iFC between aDMN and ipDMN as well as between aDMN and spDMN, suggesting an increased FC within the DMN. Patients showed increased inter-iFC between aDMN and rvCEN as well as between spDMN and rvCEN, indicating increased FC between the DMN and CEN. All significant results were due to
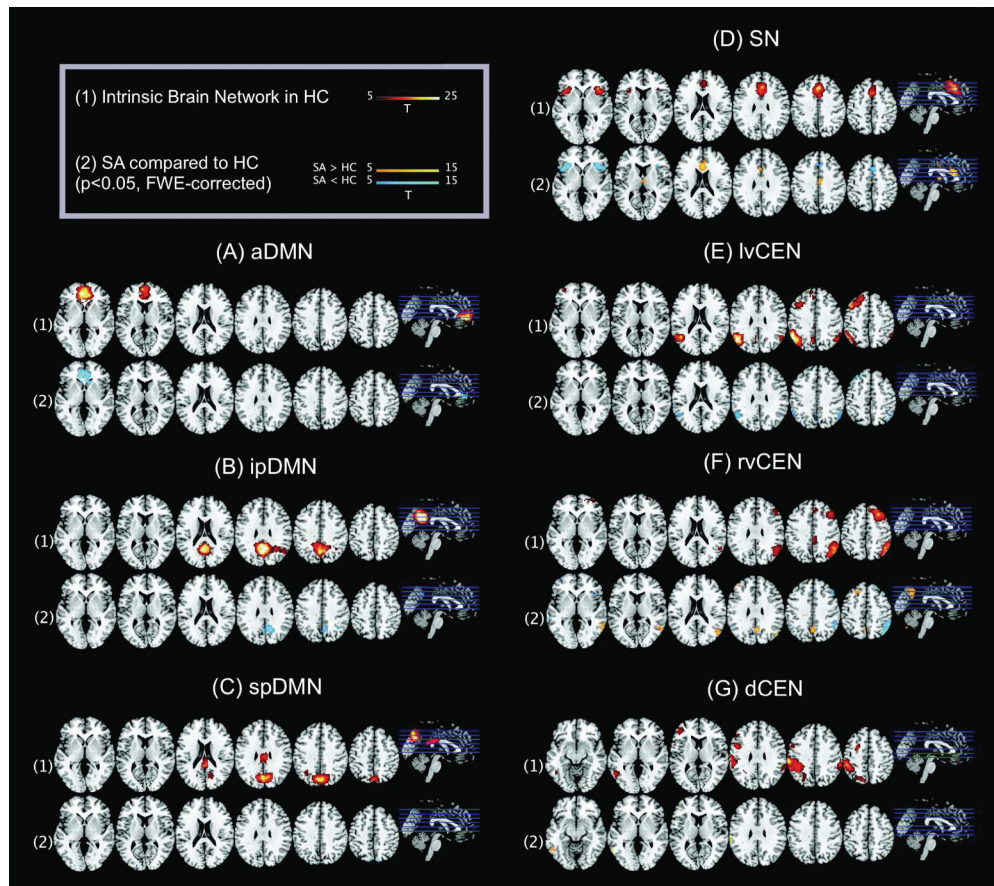
Fig. 1. Default mode, salience, and central executive network for healthy controls and corresponding group differences for patients with schizophrenia. Resting-state fMRI data were decomposed by independent component analysis (ICA). Resulting subject-specific ICs include both spatial z-maps reflecting component's functional connectivity pattern across space and time courses reflecting component's activity across time. (1) Spatial maps of selected ICs representing the default mode, salience, and central executive network (DMN, SN, CEN) were entered into voxel-wise one-sample t tests across individuals of each group and thresholded at $P < .05$, corrected for family wise error (FWE). Statistical parametric maps (SPMs) representing brain areas with significantly co-varying activity were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 25; only maps of healthy controls are shown). (2) To analyze between-group differences, controls' and patients' ICs of the DMN, SN, and CEN were entered into voxel-wise 2-sample t test with age, sex and total GM volume as covariates of no interest and thresholded at $P < .05$, FWE-corrected. SPMs were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 15). SA, group of patients with schizophrenia during acute psychosis; HC, healthy control group; a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN.

higher positive correlations in patients compared with lower positive correlations in healthy controls. Patients did not show altered inter-iFC between the SN and any other ICN.

Aberrant Temporal Dependency Between SN and DMN/CEN in Psychosis

To evaluate suggested aberrant temporal dependencies between the SN and all other ICNs, a time-lagged correlation analysis was performed on ICNs′ TCs centered on SN′s temporal activity (figure 3, table 2; $P < .05$). For lag=1, patients showed reduced time-lagged correlation between SN and both spDMN and dCEN as well as a trend for the aDMN ($P = .068$). For lag=2 patients showed reduced time-lagged correlation between SN and

both spDMN and dCEN. For lag=3, patients showed a trend to reduced time-lagged correlation between SN and spDMN ($P = .062$).

Right Anterior Insula′s Aberrant SN Connectivity Is Associated With Both DMN-CEN Interaction Changes and Psychosis Severity in Patients

To study the influence of insular SN activity on both DMN–CEN interaction increases and psychotic symptoms in patients, we correlated eigenvariates of SN's right and left AI group difference clusters with Fisher-z-transformed correlation-coefficients of each pair of network TCs or PANSS scores for hallucinations and delusions, respectively (figure 4, table S4, table S5; $P < .05$, Bonferroni-corrected). In patients,
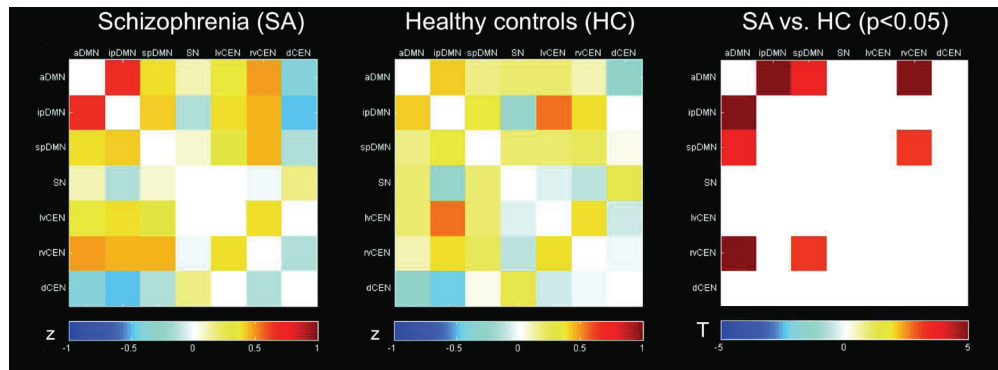
Fig. 2. Inter-network intrinsic functional connectivity matrix for patients with schizophrenia and healthy controls. *Left and middle panel:* Pairwise Pearson's correlations between time courses of the default mode, salience, and central executive network (DMN, SN, CEN) were Fisher-z-transformed, averaged across subjects for each group of patients with schizophrenia and healthy controls, and presented in a correlation matrix. Colors represent intensity of averaged z-scores. *Right panel:* To asses between-group differences, Fisher-z-transformed correlation coefficients were entered into 2-sample t tests. Tests were thresholded $P < .05$, Bonferroni-corrected for multiple comparisons and corrected for age, sex, and total GM volume. Only significant between-group differences are shown and T scores coded by color, with yellow to red representing patients>controls. a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN.

SN's right AI intra-iFC correlated negatively with inter-iFC between aDMN and rvCEN ($r = -.80$). Additionally, SN's right AI's intra-iFC correlated negatively with hallucinations ($r = -.67$). There was no further significant correlation of SN's right or left AI intra-iFC, respectively, with either inter-iFC scores or behavioral scores.

Impaired DMN-CEN Interactions Are Selectively Associated With Psychosis Severity

To study the relationship of further network interactions with psychosis severity, we correlated inter-iFC scores with PANSS-sub-scores for hallucinations and delusions (figure 4, table S6; $P < .05$, Bonferroni-corrected). Inter-iFC between aDMN and rvCEN correlated positively with hallucinations ($r = .78$). There was no further significant correlation of inter-iFC across network pairs with behavioral scores.

Discussion

To test our hypothesis that aberrant insula and DMN/CEN activity in schizophrenia is associated with an impaired dependence of DMN/CEN activity on insular SN during psychosis, resting-state fMRI was used to study within- and between-network interactions in healthy controls and patients. Beside aberrant SN, DMN, and CEN activity, patients' temporal dependence of DMN/CEN activity on SN activity was impaired. Additionally, patients' disrupted intra-iFC of the right anterior insular SN was associated with both increased inter-iFC of DMN/CEN interaction and the severity of hallucinations. These findings extend our knowledge about insular dysfunction in schizophrenia by

demonstrating a link between disordered right anterior insula, DMN, CEN, and psychosis. Results are consistent with the view that aberrant insula salience processing is related with impaired insula control function of DMN/CEN interactions in psychosis.

Linking Altered Right Anterior Insular and DMN/CEN Activity in Psychosis

Driven by our hypothesis,[1,20] we found decreased temporal dependence of spDMN and dCEN activity as well as a trend to decreased temporal dependence of aDMN activity on SN activity in patients with schizophrenia during psychosis (figure 3, table 2). Patients' impaired temporal interaction of the SN was specific for time-lagged inter-iFC, because SN's inter-iFCs with DMN and CEN, respectively, were not changed in patients (table 2). Impaired dependence of DMN/CEN activity on SN activity seems to be primarily driven by the right AI: (1) SN's intra-iFC is reduced in patients' rAI (figure 1); (2) rAI's intra-iFC is associated with impaired DMN-CEN interactions (figure 4); (3) rAI's intra-iFC corresponds with severity of hallucinations (figure 4, table S5); (4) these relationships were specific for rAI, because the left anterior insula, which was also characterized by impaired intra-iFC, did not show any significant correlation with network interactions and symptoms, respectively (table S4). These results are not explained by medication or brain volume effects, which were included into the analyses as covariates of no-interest. Together, these findings demonstrate an aberrant dependence of DMN/CEN interactions on right anterior insular SN activity that is relevant for patients' hallucinations.

These results are consistent with the view that the right anterior insula´s control function for DMN/CEN

Table 2. Inter-Network Intrinsic Functional Connectivity and Time-Lagged Inter-Network Connectivity in Patients With Schizophrenia in Acute State of Psychosis and Healthy Controls

Inter-iFC	SA		HC		SA vs HC[a]	
	Mean	SD	Mean	SD	Direction	P Value
Inter-iFC						
aDMN–ipDMN	0.673	0.117	0.422	0.163	SA>HC	<.001*
aDMN–spDMN	0.402	0.207	0.181	0.145	SA>HC	<.001*
aDMN–SN	0.106	0.206	0.200	0.186	HC>SA	.201
aDMN–lvCEN	0.366	0.169	0.215	0.168	SA>HC	.024
aDMN–rvCEN	0.477	0.145	0.111	0.174	SA>HC	<.001*
aDMN–dCEN	−0.398	0.182	−0.312	0.141	HC>SA	.136
ipDMN–spDMN	0.424	0.276	0.368	0.247	SA>HC	.431
ipDMN–SN	−0.137	0.170	−0.221	0.197	SA>HC	.186
ipDMN–lvCEN	0.392	0.258	0.554	0.185	HC>SA	.044
ipDMN–rvCEN	0.444	0.176	0.383	0.153	SA>HC	.180
ipDMN–dCEN	−0.487	0.220	−0.449	0.173	HC>SA	.709
spDMN–SN	0.064	0.192	0.211	0.194	HC>SA	.014
spDMN–lvCEN	0.302	0.257	0.207	0.246	SA>HC	.458
spDMN–rvCEN	0.464	0.272	0.226	0.180	SA>HC	.001*
spDMN–dCEN	−0.133	0.222	0.051	0.195	HC>SA	.006
SN–lvCEN	0.019	0.214	−0.046	0.254	SA>HC	.467
SN–rvCEN	−0.031	0.206	−0.109	0.239	SA>HC	.247
SN–dCEN	0.182	0.188	0.265	0.185	HC>SA	.086
lvCEN–rvCEN	0.382	0.227	0.383	0.211	HC>SA	.774
lvCEN–dCEN	0.031	0.149	−0.080	0.186	SA>HC	.093
rvCEN–dCEN	−0.156	0.201	−0.008	0.191	HC>SA	.020
Time-lagged inter-iFC						
Lag=1						
SN–aDMN	0.055	0.180	0.182	0.185	HC>SA	.068
SN–ipDMN	−0.096	0.157	−0.163	0.186	SA>HC	.231
SN–spDMN	0.043	0.162	0.170	0.169	HC>SA	.012*
SN–SN	1.028	0.190	1.061	0.130	HC>SA	.258
SN–lvCEN	0.038	0.210	0.013	0.241	SA>HC	.795
SN–rvCEN	−0.029	0.199	−0.046	0.213	SA>HC	.634
SN–dCEN	0.129	0.183	0.249	0.187	HC>SA	.023*
Lag=2						
SN–aDMN	−0.013	0.171	0.080	0.194	HC>SA	.192
SN–ipDMN	−0.048	0.143	−0.074	0.162	SA>HC	.531
SN–spDMN	0.001	0.132	0.088	0.144	HC>SA	.025*
SN–SN	0.377	0.230	0.411	0.139	HC>SA	.290
SN–lvCEN	0.038	0.195	0.043	0.198	HC>SA	.884
SN–rvCEN	−0.035	0.162	−0.012	0.162	HC>SA	.894
SN–dCEN	0.078	0.181	0.182	0.169	HC>SA	.030*
Lag=3						
SN–aDMN	−0.035	0.148	0.003	0.174	HC>SA	.591
SN–ipDMN	−0.041	0.108	−0.013	0.137	HC>SA	.535
SN–spDMN	−0.031	0.124	0.341	0.131	HC>SA	.062
SN–SN	0.157	0.229	0.171	0.128	HC>SA	.502
SN–lvCEN	0.035	0.177	0.039	0.157	HC>SA	.901
SN–rvCEN	−0.021	0.116	−0.005	0.135	HC>SA	.888
SN–dCEN	0.045	0.166	0.106	0.129	HC>SA	.120

Note: inter-iFC, inter-network intrinsic functional connectivity; time-lagged inter-iFC, time-lagged inter-network intrinsic functional connectivity; a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN; SN, salience network.

[a]2-sample t test controlled for age, sex and total GM volume. inter-iFC.

*significant for $P < .05$, Bonferroni-corrected for multiple comparisons (n = 21); time-lagged inter-iFC: *significant for $P < .05$.

interactions is impaired in schizophrenia. Three types of previous findings support this interpretation: structural and functional changes of the anterior insula in schizophrenia;[2] the critical role of rAI activity in switching DMN and CEN activity;[18,19] models suggesting impaired anterior insular control function in patients with schizophrenia.[1,20] However, one of our findings relies on time-lagged iFC analysis. Although
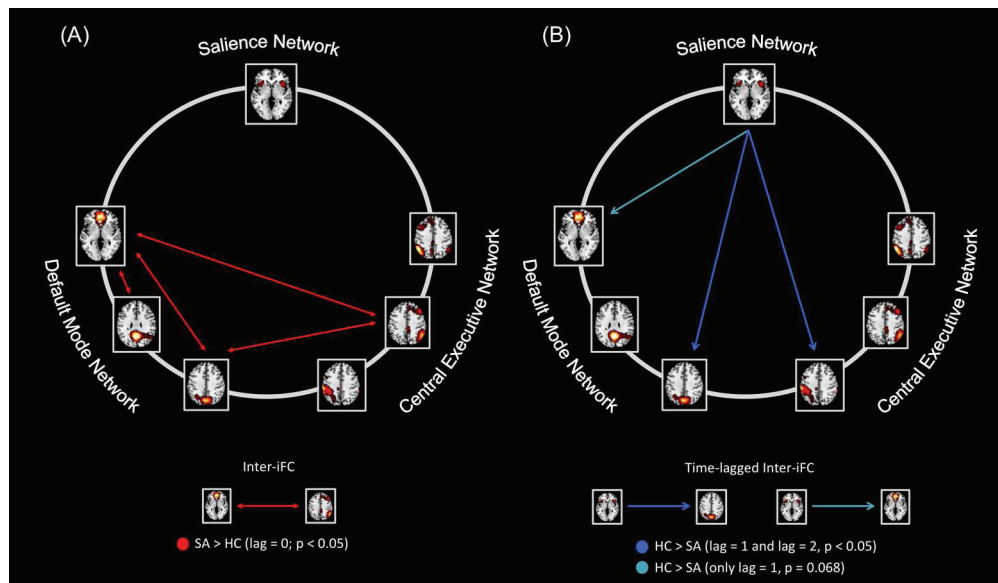
Fig. 3. Between-group differences of both inter-network intrinsic functional connectivity and time-lagged connectivity in patients and healthy controls. Spatial maps (derived from figure 1) indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). Based on network time courses, inter-network intrinsic functional connectivity (inter-iFC) and corresponding time-lagged connectivity (lagged inter-iFC) were calculated by the use of Pearson's correlation between subject specific ICN time courses (TCs) and time-lagged ICNs' TCs centered on SN's temporal activity. Panel A: Red arrows indicate increased inter-iFC of patients compared with healthy controls (2-sample t test, $P < .05$, Bonferroni-corrected for multiple comparisons). Panel B: Blue arrows indicate decreased time-lagged correlation of patients compared with healthy controls for lag=1 and lag=2 (2-sample t test, $P < .05$). The tourqoise arrow indicates decreased time-lagged correlation of patients compared with healthy controls for lag=1 only (2-sample t test, $P = .068$). All tests were corrected for age, sex and total GM volume. Abbreviations: SA, group of patients with schizophrenia during acute psychosis; HC, healthy control group.

time-lagged analysis is often performed,[29,32,33] it is still a subject of debate how lagged-iFC relates with directional influence of potential control networks/areas[34,35] (for detailed discussion, see the online supplementary material). For example using simulated resting-state-fMRI data and lagged-iFC approaches, Smith and colleagues had problems to achieve accurate estimations of iFC direction.[34] However, Schippers and colleagues demonstrated for a large data sample robust and sensitive performance of time-lagged-iFC analysis to identify directional influence.[35,36,37] More studies are necessary to further analyze the relationship between cognitive control, directional connectivity and insular resting-state lagged-iFC in schizophrenia (eg combined task- and rest-fMRI to study insula effective connectivity and its relationship with lagged iFC at-rest in patients with psychosis). Remarkably, only the right AI was linked to both DMN/CEN interactions and symptoms, indicating an asymmetric insular involvement in psychosis. This asymmetry reflects previous findings, which relate particularly the rAI with interoceptive feelings and the asymmetric representation of afferent sympathetic nervous system activity.[8] Therefore, our data might indicate a potential link between aberrant rAI control processes, sympathetic activity and interoception in psychosis.

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DMN-CEN Inter-Network Interactions Are Altered in Psychosis and Associated With the Severity of Hallucinations

1. Regarding DMN, decreased intra-iFC was found in ACC and medial posterior parietal cortex (figure 1). Across 3 ICNs representing the DMN, inter-iFC was increased, specifically between the aDMN and both ipDMN and spDMN (figures 2 and 3). Altered activity within the DMN has been consistently reported in patients with schizophrenia during a broad range of tasks.[11] During rest, recent fMRI studies demonstrated inconsistent results, including both increased[12] and decreased DMN intra-iFC[38] in patients with schizophrenia. It has been suggested, that this discrepancy might be explained by different methodological approaches and patient samples.[39] Here, we choose a high-order-model ICA, decomposing the DMN in 3 intrinsic brain networks, each representing a distinct subsystem of the DMN. DMN subsystems demonstrated both decreased iFC within (figure 1) and increased iFC across subsystems (figures 2 and 3). Our finding of increased and decreased DMN iFC based on DMN subsystems may help to explain previous inconsistent results of aberrant DMN integration at rest in schizophrenia.

2. Regarding CEN, we found between-group differences for CEN's intrinsic FC, including decreased
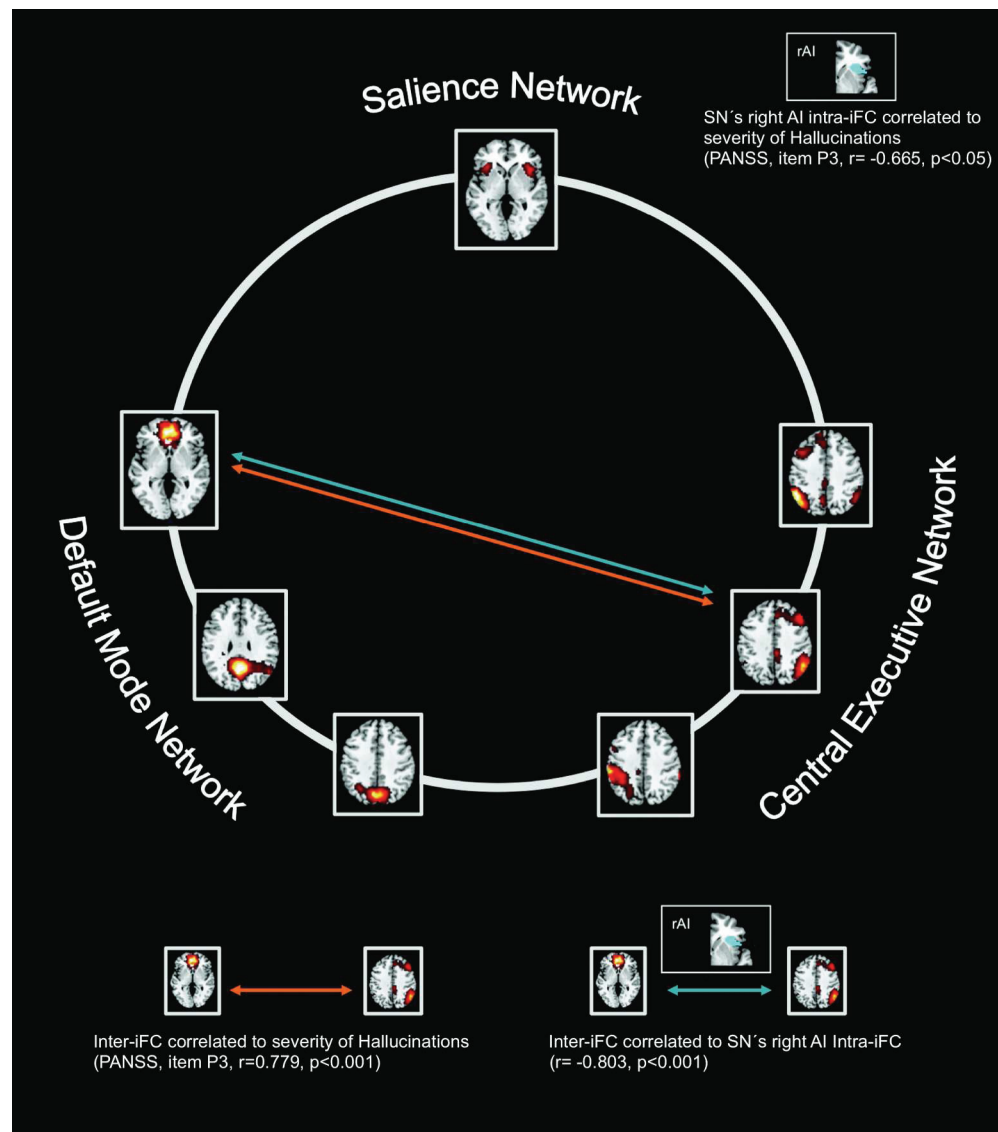
Fig. 4. Patients' right anterior insular SN activity is associated with increased DMN-CEN interaction and severity of hallucinations. Spatial maps (derived from fig. 1) indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and SN. Based on time courses of these networks, inter-network intrinsic functional connectivity (inter-iFC) was calculated by the use of Pearson's correlation. In patients, averaged right anterior insular SN activity (insert with turquoise spatial map) was significantly correlated with both inter-iFC scores (panel right below; turquoise arrow; partial correlation, $P < .05$) and hallucination scores of PANSS (panel right above; partial correlation, $P < .05$). Further, patients' severity of hallucinations was positively correlated with inter-iFC between aDMN and rvCEN (Panel left below; orange arrow; partial correlation, $P < .05$). Partial correlations were corrected for age, sex, total GM volume, and medication.

intra-iFC in bilateral inferior parietal lobule and frontal gyrus and increased intra-iFC in the right angular gyrus (figure 1). CEN disruption is characteristic for several psychiatric disorders, including schizophrenia.[20] Recently, Woodward and colleagues[40] demonstrated mainly reduced CEN connectivity in patients with schizophrenia. Rotarska-Jagiela and colleagues found increased and decreased intra-iFC during rest in patients' lateralized CENs.[15]

Taken 1 and 2 together, our results support the robust impact of schizophrenia on DMN/CEN and demonstrate the representative nature of our study sample.

3. Regarding the inter-iFC between DMN and CEN, we found strongly increased synchronous activity between aDMN and rvCEN as well as between spDMN and rvCEN (figures 2 and 3). Furthermore, increased inter-iFC between aDMN and rvCEN correlates selectively with the severity of hallucinations (figure 4, table S6). This perfectly corresponds with recent results,[16] demonstrating inappropriate engagement and disengagement of anticorrelated intrinsic brain networks in schizophrenia.[17] More generally, it has been suggested that impaired anticorrelated relationship between task-positive CEN and task-negative DMN may be a characteristic feature

of schizophrenia.[17] Here we extended these findings by demonstrating that impaired DMN/CEN interactions are related with impaired anterior insular SN.

Further Points and Limitations

To evaluate the study's result more accurately, several methodological issues have to be considered, including the use of ICA, the ongoing debate about hemodynamic lag analysis, and the potential influence of patients' medication on results. A detailed discussion of these points is presented in the online supplementary material.

Psychopathological Implications

What are potential implications of aberrant insular network interaction to understand psychotic symptoms? The dependence of DMN/CEN interactions on both the activity of the SN and connectivity of the right anterior insula within the SN suggests that interactions of self- and external-task-related processes depend on processes that assign emotional salience to objects, people, and events.[19] This assignment and its learning is impaired in schizophrenia.[1,9,10,33] In patients, aberrant salience processing may bias interacting self- and external-task-related processes via impaired insular control function on DMN/CEN interactions. Salience-dependent bias, in turn, may contribute to psychotic perceptions and constructs of the patient. Further studies including task- and resting-state fMRI are necessary to test these suggestions.

Conclusion

We found evidence that in schizophrenia impaired anterior insula SN activity is associated with an aberrant dependence of DMN/CEN interactions on SN activity. This finding suggests a link between aberrant insula salience activity, DMN, CEN, and psychosis in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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