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Resting-state hyperconnectivity of the anticorrelated intrinsic networks in schizophrenic patients and their unaffected siblings

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Abstract

RESTING-STATE HYPERCONNECTIVITY OF THE ANTICORRELATED INTRINSIC NETWORKS IN SCHIZOPHRENIC PATIENTS AND THEIR UNAFFECTED SIBLINGS.

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Abnormal connectivity of the intrinsic anticorrelated networks, the task-negative network (TNN) and task-positive network (TPN), is implicated in schizophrenia. Comparisons between schizophrenic patients and their unaffected siblings offer an opportunity to further understand illness susceptibility and pathophysiology. We hypothesized that schizophrenic patients would demonstrate hyperconnectivity in the intrinsic networks and that similar, but less pronounced, hyperconnectivity would be evident in the networks of the unaffected siblings. Resting-state functional magnetic resonance images were obtained from schizophrenic patients (n=25), their unaffected siblings (n=25), and healthy controls (n=25). The posterior cingulate cortex/precuneus (PCC/PCu) and right dorsolateral prefrontal cortex (DLPFC) were used as seed regions to identify the TNN and TPN. Interregional connectivity strengths were analyzed using overlapped intrinsic networks composed of regions common to the intrinsic networks of the three subject groups. In the TNN, schizophrenic patients alone demonstrated hyperconnectivity between the PCC/PCu and left inferior temporal gyrus and between the ventral medial prefrontal cortex and the right lateral parietal cortex. Both schizophrenic patients and their unaffected siblings showed increased connectivity in the TNN between the bilateral inferior temporal gyri. In the TPN, schizophrenic patients showed hyperconnectivity between the left DLPFC and right inferior frontal gyrus relative to unaffected siblings, though this trend only approached statistical significance in comparison to healthy controls. Resting-state hyperconnectivity of the intrinsic networks may underlie the pathophysiology of schizophrenia by disrupting network coordination. Similar, though milder, hyperconnectivity in unaffected siblings of schizophrenic patients may contribute to their cognitive deficits and increased risk to develop schizophrenia.

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Introduction

Disconnection Hypothesis

While the precise pathophysiology of schizophrenia remains to be elucidated, there has been long-standing interest in the hypothesis that schizophrenia is an illness of aberrant connectivity within distributed brain networks. This theory was put forth as early as 1906, when Wernicke proposed that the disruption of fiber tracts was responsible for psychosis [1]. Subsequent work by Bleuler repositioned the disconnection in terms of cognitive functions, as he coined the term "schizophrenia" to refer to the lack of integration between mental functions such as thought, emotion, and behavior [2]. Finally, the disconnectivity hypothesis in its modern incarnation was formulated by Friston, who postulated that schizophrenia involves abnormal modulation of synaptic plasticity such that schizophrenia "symptoms are not due to a single regionally specific pathophysiology but are expressed when two or more regions interact" [3].

Research supporting such a conclusion is provided by a number of different modalities, and the disconnection hypothesis is increasingly becoming the dominant theory in schizophrenia research. For example, multiple positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have identified abnormal functional connnectivity, and these distortions have been found in connections throughout the brain, including fronto-temporal [4-6] [7], fronto-parietal [8], dorsolateral prefrontal-hippocampal [6], and in the cortico-cerebellar-thalamo-cortical circuit [9, 10]. Functional disconnectivity is further demonstrated in schizophrenia in a number of electroencephalographic (EEG) and magnetoencephalographic (MEG) studies during

both the resting-state and task performance [11, 12 13-19]. Functional connectivity and synaptic plasticity are intimately linked given the fact that it is synaptic plasticity that enables interregional connectivity to develop and adapt [20, 21]. Therefore, the multitude of studies in schizophrenia research that reveal abnormal synaptic plasticity lend additional support to the disconnection hypothesis and provide a model at the cellular level for its generation [7, 22]. Moreover, structural studies of white matter volume indicate decreased total WM volume and specific decreases in frontal and callosal volume associated with schizophrenia [23, 24]. Diffusion tensor imaging, an MRI technique that allows the exploration of the microstructural integrity of white matter fibers, has revealed widespread white matter deficits, with abnormalities consistently noted in the frontal, temporal, callosal, and cingulate regions [25, 26]. Finally, neural network computer simulations of schizophrenia examine alterations in connectivity to offer a neurobiological explanation for the genertaion of auditory hallucinations [27]. Neuroscience research in recent years is increasingly addressing the geographically disparate functional networks of the brain rather than focusing on specific anatomical structures [28], and there has been growing interest in the role that abnormal connectivity of such networks may play in schizophrenia [3, 22].

Intrinsic Anticorrelated Networks

In particular, there has been growing interest in the brain's resting-state, its relationship to task performance, and the neural networks that underlie these cognitive functions [29, 30]. The concept of a default-mode network emerged accidentally from early neuroimaging studies that focused on task performance and used the resting mode as a control state. Interestingly, these studies, in addition to showing the expected increases in

regional activity, identified a set of regions that were consistently deactivated during the performance of tasks. In a meta-analysis, Shulman *et al.* compiled data from 132 subjects scanned by PET and compared scans acquired during active task performance to scans acquired during passive task performance [31]. Similarly, Mazoyer *et al.* conducted a meta-analysis of PET scans acquired either during task performance or at rest [32]. The results in these studies were remarkably similar to each other, as each identified a set of brain regions that was more active at rest than during task performance (regardless of the nature of the task) [31, 32]. Anatomically, these task-related decreases in activity were observed in the posterior cingulate cortex/precuneus (PCC/PCu), the medial prefrontal cortex (MPFC), bilateral inferior temporal gyri (ITG), and bilateral parietal cortices [31, 32].

Further support for the existence of a functional network incorporating these regions was supplied by two fMRI techniques. First, rapid event related fMRI enables analysis of task-related changes in brain activity in a faster time frame than is possible by PET scanning [33]. A meta-analysis of this technique by Shannon *et al.* identified a set of regions with task-related deactivations that mirrored the PET findings [34]. Second, functional connectivity MRI analyzes the temporal correlation between spontaneous activity fluctuations in different brain regions to assess connectivity and has the advantage of allowing connectivity to be assessed during the resting-state [35, 36]. Using this method, numerous studies have identified a set of regions deactivated by task performance that closely matches the PET findings of Shulman *et al* [29, 30, 33, 37-42]. Because these regions were more active during the resting-state than during task performance, they were collectively termed the default-mode network or "task negative" network (TNN) and it was hypothesized that reduction of their tonic activity represented

the temporary redistribution of resources to address momentary tasks [29, 41]. Finally, in addition to the default-mode network, the functional connectivity analysis also demonstrated the presence of an anticorrelated, functionally competitive network composed of regions that were activated during tasks and termed the task-positive network (TPN) [30, 37]. Like the TNN, this network was evident during both task performance and in the resting-state.

Functionally, the TNN has been hypothesized to underlie cognitive processes that focus primarily on the internal world while maintaining baseline external monitoring [33, 43, 44]. It is thought that the TNN underlies "self-reflective and self-referential mental activity" and is engaged in processes such as simulating behavior and planning for the future [38, 45]. A particular form of this activity that has received considerable attention is the production of stimulus-independent thoughts (SIT's) or mind-wandering [44, 45]. The relationship between the TNN and SIT's is supported by fMRI studies in which increased activity of the regions of the TNN is associated with increased production of SIT's [46] and in which individuals with the greatest TNN activity were most likely to have their minds wander [44]. SIT's most commonly occur in the context of memory, and recent research suggests that they play a role in offline memory processing [47]. Moreover, the TNN integrates emotional and cognitive inputs into the decision making process [48-50], and thus may play a role in balancing the response to varying stimuli [51]. In addition to these inwardly directed functions, the TNN is thought to broadly monitor the external world. In this "sentinel hypothesis," the TNN maintains a low level awareness without actively exploring any feature or task [31, 33]. Such a function is supported by the fact that the TNN is active in detecting targets that are randomly presented at multiple locations but not

active when the targets were presented only a specific location [52]. This baseline attention thus enables the salience of the stimulus to be determined such that it can be further investigated if necessary [43].

The second resting state network consists of brain regions that demonstrate increased activity in association with task performance. It bilaterally includes the dorsolateral prefrontal cortex (DLPFC), middle temporal region (MT), insula, supplementary motor area, and inferior temporal lobule (ITL) [37]. The TPN is responsible for task-orientation and the top-down modulation of attention [53]. As such, it underlies sustained attention, selective attention, and stimulus-response attention that requires modulation of conflict [39, 54-56]. In addition, the TPN is involved in selecting appropriate responses to environmental stimuli and planning and preparing for willful acts [57, 58].

An important property of the intrinsic networks, the TNN and the TPN, is that they are anticorrelated [37]; that is, the functional organization of these opposing networks is such that increased activity of the TPN corresponds to decreased activity of the TNN and vice versa. It is therefore proposed that the brain alternates between introspection, as characterized by activity in the TNN, and extrospection, as characterized by activity in the TPN [38]. The anticorrelation of these networks thus mediates the interaction between these functionally competitive systems in order to separate contrasting neuronal processes [37]. This theory is supported by the fact that increased task difficulty, corresponding to increased TPN requirements, is associated with decreased production of stimulus-independent thoughts (SIT's), corresponding to increased TNN deactivation [59]. The importance of proper network coordination to optimal cognitive functioning was emphasized by a study in which increased frequency of SIT's during a cognitive task was

associated with decreased performance [60]. Sonuga-Backe *et al*. have coined the "default-mode interference hypothesis" to explain failure of top-down control as a failure to transition fully from the default-mode to a cognitive task-processing mode [58]. Finally, low frequency oscillations synchronizing activity in these networks are evident during the resting-state, during which the anticorrelation persists [37]. Thus, functional connectivity is essential not only to communication within the TNN and TPN themselves, but also to the anticorrelation between these networks.

Given the relevance of the intrinsic network functions to schizophrenia, there has been increasing interest in the role that altered connectivity of these networks may play in the illness [61]. For example, it has been proposed that deficits in self-monitoring, a function of the TNN, may be implicated in many of the positive symptoms of schizophrenia [62]. The TNN is involved in differentiating between internal and external sources of information and abnormalities of this network are implicated in the generation of hallucinations [63]. Indeed, neuroimaging studies of patients with active hallucinations have demonstrated activity in regions of the TNN including the orbitofrontal cortex and the cingulate cortex [64]. Cognitive deficits, such as impaired working memory, attention allocation, and central executive function, are not only core symptoms of schizophrenia [65] but also are functions ascribed to the TPN [39, 57]. Finally, numerous studies in schizophrenia have identified abnormalities in the regions that make up both the TNN and the TPN [66-68]. Our early studies using the blood oxygen level dependent (BOLD) signal analysis detected abundant connectivity and activity abnormalities in schizophrenic patients, with widespread decreased connectivity as the most consistent finding [66, 69, 70]. When we focused our analysis on the intrinsic networks, however, we

found increased connectivity in the TNN, both increased and decreased connectivity in the TPN, and increased anticorrelation between the TNN and the TPN [42]. These findings suggest that examining the connectivity and coordination of both of the anticorrelated intrinsic networks may improve our understanding of their roles in schizophrenia susceptibility and pathophysiology.

Unaffected Relatives of Schizophrenic Patients

Strong evidence for a genetic contribution to schizophrenia includes concordance rates of 41-65% in identical twin pairs and heritability estimates of 80-85% [71]. The precise genes involved in increased susceptibility to schizophrenia remain unknown, and it is hypothesized that the mode of inheritance is complex [72-74]. Endophenotypes are intermediate markers between disease genetics and the observable phenotype, and it is hoped that identification of these biological markers will focus the search for schizophrenia genes by elucidating which neurobiological processes are involved [75]. Research in unaffected siblings of schizophrenic patients may aid this endeavor because these individuals share a genetic background with schizophrenic patients and have an approximately 10-fold higher risk to develop schizophrenia than the general population [76]. Relatives of schizophrenic patients exhibit brain abnormalities including decreased hippocampal volume [77] and altered activity patterns in the prefrontal cortex and right parietal cortex [78]. In addition, these individuals have cognitive deficits that are similar to, but milder than, those of schizophrenic patients in domains such as continuous performance, auditory verbal learning [79], executive function, verbal memory recall [80], and episodic memory [81, 82]. While these abnormalities indicate deficits of brain function in

the unaffected relatives, to date few reliable biomarkers have been developed. Finally, because unaffected siblings are comparatively free of confounding factors, such as antipsychotic medications, substance abuse, and institutionalization, that can complicate findings from schizophrenic patients, data from unaffected siblings may both elucidate illness endophenotypes and provide insights into the pathophysiology of schizophrenia.

Functional Connectivity Analysis

Functional connectivity analysis is based on changes in regional blood flow and oxygen availability in the brain. It has long been known that increased neuronal activity is associated with increases in regional blood flow, and this relationship forms the basis of PET analysis. As the study of these changes progressed, it emerged that the change in oxygen consumption during neuronal activation was not as marked as the increase in regional blood flow [83]. Therefore, the amount of oxygen available in the blood can be used as a marker of neuronal activity, as increased neuronal activity corresponds with a decreasing proportion of oxygen extracted from the blood [29]. The oxygenation of hemoglobin is readily detectable by MRI [84], meaning that this technique can be used to monitor the amount of oxygen available in the blood. In 1990, Ogawa *et al*. termed this the blood-oxygen-level dependent (BOLD) signal [85] and were the first to show that this technique could be used as a correlate of neuronal activity [86, 87]. This methodology was quickly adopted by other researchers [88, 89] and became the basis for functional MRI (fMRI). Recently, there has been increasing interest in the use of fMRI during the resting-state, leading to confirmation that functional neuronal systems can be detected even in the absence of task performance based on high temporal correlation in the

spontaneous low frequency (<0.1 Hz) fluctuations of the BOLD signal [35, 90, 91]. In 2003, Greicius *et al*. were the first to demonstrate that the TNN could be detected by fMRI in the resting-state, and they also showed an inverse correlation between activity in the TNN and activity in task-oriented regions in the lateral prefrontal cortex [30]. Fox *et al*. extended this work to map functional connectivity of both the TNN and the TPN in the resting-state and to establish anticorrelation of these competing networks [37]. Thus, BOLD signal analysis in the resting-state can be used to analyze the functional connectivity of the intrinsic anticorrelated networks that may be implicated in the pathophysiology of schizophrenia.

Statement of purpose, specific hypothesis, and specific aims of the thesis

In the present study, we sought to examine the resting-state functional connectivity differences in the intrinsic networks between schizophrenic patients, their unaffected siblings, and healthy controls. We hypothesized that schizophrenic patients would demonstrate hyperconnectivity in the intrinsic networks and that similar, but less pronounced, hyperconnectivity would be evident in the networks of unaffected siblings of schizophrenic patients. Using our previously published methods [42], we identified the intrinsic networks in each subject group on the basis of correlation with predefined seed regions. We then created overlapped networks consisting of the regions that were common to the intrinsic networks in each subject group. Finally, interregional connectivity was compared between the three subject groups.

Methods

Participants

Patients with the clinical diagnosis of schizophrenia were recruited from the Department of Psychiatry, Second Xiangya Hospital of Central South University, Changsha, China. Patients were included if, after evaluation by the Structured Clinical Interview for DSM-IV (SCID), Patient version [92], they met the DSM-IV diagnostic criteria for schizophrenia and had at least one unaffected sibling. Patients were excluded if they had any history of neurological disorder, severe medical disorder, substance abuse (nicotine was not considered), or electroconvulsive therapy.

Neither the unaffected siblings nor the healthy controls met the DSM-IV criteria for any Axis-I psychiatric disorders as assessed by the SCID non-patient version. Healthy controls were recruited from the Changsha City area and had no first-degree relatives with a history of psychotic disorders. Data on the gender, age, handedness, and education level of each patient, sibling, and control was collected. Data on the course of illness and medication history for each patient with schizophrenia was collected.

All participants gave their written informed consent to participate in the study after the risks and benefits were discussed in detail. The study was approved by the ethics committee of the Second Xiangya Hospital, Central South University.

Instruction to participants

Before scanning, the participants were explicitly instructed to lie supine, stay relaxed with their eyes closed, and move as little as possible.

Image acquisition

Images were acquired on a 1.5-T GE Signa Twinspeed scanner (General Electric Medical System, Milwaukee, USA). A standard head coil was used for radio frequency transmission and reception of magnetic resonance signal. Foam pads and earplugs were used to minimize head motion and scanner noise, respectively. Functional images were acquired by using a gradient-echo echo-planar imaging sequence sensitive to BOLD signal (repetition time (TR)/echo time (TE)=2000/40ms, flip angle=90°, field of view (FOV)=24x24 cm^2, matrix 64x64). Whole-brain volumes were acquired with 20 contiguous 5mm thick transverse slices with a 1mm gap and 3.75mm×3.75mm in-plane resolution. For each participant, the fMRI scanning lasted for 6 minutes. T1-weighted images (TR/TE=2045/9.6 ms, flip angle=90°, FOV=24x24 cm^2, matrix 64x64) were acquired at the same location as the functional images in order to acquire anatomical information.

Image preprocessing

The SPM2 software (Wellcome Department of Imaging Neuroscience, London, UK) was used for image preprocessing. The first 10 volumes of each functional time series were discarded for scanner calibration and for participants to become accustomed to their surroundings. The remaining 170 volumes were corrected for the acquisition delay between slices and for head motion. All the images of each participant met the following two conditions: (1) maximum displacement in x, y or z was less than 2mm and (2) angular rotation about each axis was less than 2°. Because correlation analysis is

sensitive to gross head motion effects, we further characterized the peak displacements as a measure of head motion for each participant [90]. The images were then stereotactically normalized into the standard space defined by the Montreal Neurological Institute (MNI) template, re-sampled to 3×3×3mm3, and smoothed spatially with a Gaussian kernel of 4 mm full-width-at-half-maximum (FWHM). To reduce the effects of confounders, six motion parameters, linear drift, and the mean time series of all voxels in the whole brain were removed from the functional data through linear regression. Then the functional data were band-pass filtered (0.01-0.08 Hz) using AFNI software (http://afni.nimh.nih.gov/) [37, 90].

Identification of the anticorrelated intrinsic networks

Definition of seed regions

The WFU_PickAtlas software (http://www.ansir.wfubmc.edu) [93] was used to generate the seed regions necessary to constitute the intrinsic networks. The R.DLPFC refers to Broadmann area 46 (BA46) in the right middle frontal gyrus, and the PCC/PCu refers to BA31 in the bilateral posterior cingulate cortices and the adjacent precuneus. These two regions are important nodes in the TPN and TNN respectively and have been observed to play vital roles in resting-state brain function [30, 53]. We have previously used the functional connectivities of these two regions to identify the intrinsic networks [42]. In this study, we averaged the BOLD time series of the voxels within each seed region to obtain the reference time series for the seed region.

Correlation maps of seed regions

For each participant and each seed region, we computed the correlation coefficients between the seed region's time series and the time series of all voxels in the brain. The correlation coefficients were converted to z values using Fisher's r-to-z transform in order to improve the normality. One-sample t-test was performed in a voxel-wise manner on the individual z-values data to determine which brain regions were significantly correlated with the seed region. The False Discovery Rate (FDR) [94] procedure was used to control the expected proportion of false positive at p=0.05. A minimum cluster size of 30 voxels was set for the identified brain regions, and the positive and negative correlation maps of each seed region were obtained for each group.

Construction of the intrinsic networks

The ImCalc toolbox of the SPM2 was used to construct the intrinsic networks for the patient, sibling, and control groups. For each group, the composition of the TNN was obtained by intersecting the brain regions significantly positively correlated to the PCC/PCu with those significantly negatively correlated to the right DLPFC. Similarly, the composition of the TPN was obtained by intersecting the regions significantly positively correlated to the right DLPFC with those significantly negatively correlated to the PCC/PCu. An overlapped network composed of regions present in the intrinsic networks of all study groups was generated by creating a binary mask for each subject group in which each voxel value was set to one if the voxel belonged to the intrinsic networks and set to zero if it did not. Thus a patient mask, a sibling mask, and a control mask were generated separately. These three masks were then intersected to obtain the

overlapped mask.

Interregional functional connectivity analyses in the intrinsic networks

The regions of the overlapped network were used as seed regions for the interregional functional connectivity analysis. For each group, the mean time series of each region was obtained by averaging the BOLD time series over all the voxels in the region. Pearson's correlation coefficients were computed between each pair of these seed regions. After Fisher's r-to-z transform, individual z-values were entered into the following analysis.

The connectivity among the three groups was considered to be significantly different if: (1) the z-values of this connectivity were significantly different from zero in at least one group by one-sample t-test ($p<0.05$, FDR corrected), and (2) the three groups showed significantly different z-values of this connectivity by ANOVA ($p<0.05$, corrected). We used a permutation-based correction for multiple comparisons using Ptest software by 10,000 permutations [95-98]. Then, post hoc (LSD) tests ($p<0.05$, 2-tailed) were used to examine the differences in the connectivities identified by ANOVA. Additionally, we compared each connectivity within the intrinsic networks between groups by a two-sample t-test (healthy controls vs. unaffected siblings or schizophrenia patients) and a paired t-test (unaffected siblings vs. schizophrenia patients).

Results

Participant characteristics

The 25 schizophrenic patients, their unaffected siblings, and healthy controls were well matched for sex, age, and education (Table 1). All the participants were right-handed. Six schizophrenic patients were drug naïve, while the remainder were receiving antipsychotic medications at the time of scanning (risperidone [n=10, 2-6mg/day], clozapine [n=4, 200-350mg/day], quetiapine [n=4, 400-600mg/day], sulpiride [n=1, 200mg/day]).

Identification of the intrinsic networks

By using functional connectivity analysis and an overlap strategy, we identified and validated the anticorrelated intrinsic networks in the three groups (Table 2, Figure 1). The brain regions of the TNN included the PCC/PCu, bilateral medial prefrontal cortex (MPFC), bilateral inferior temporal gyri (ITG), and right lateral parietal cortex (LPC). The regions of the TPN included the DLPFC, inferior frontal gyrus/insula (IFG), inferior parietal lobule (IPL), and supplementary motor area (SMA) bilaterally, and the dorsal premotor cortex (dPM), orbital frontal cortex (OFC) and middle temporal (MT) region on the right side of the brain only.

Connectivity differences in the intrinsic networks

Among the three groups, connectivity differences were found between the PCC/PCu and the left ITG ($F=7.077$, $p_{corrected}=0.002$), the ventral MPFC (vMPFC) and right LPC ($F=3.508$, $p_{corrected}=0.034$), the left and right ITG ($F=5.031$, $p_{corrected}=0.008$), and the left

DLPFC and right IFG (F=3.264, $p_{corrected}$=0.044) by ANOVA ($p_{corrected}$<0.05). Post hoc tests for these connectivities showed significantly higher connectivity between the PCC/PCu and left ITG and between the vMPFC and the right LPC in the schizophrenic patients compared with the unaffected siblings and the healthy controls. We also found significantly higher connectivity between the bilateral ITG in both the schizophrenic patients and the unaffected siblings compared with the healthy controls. Finally, significantly higher connectivity between the left DLPFC and IFG was found in the schizophrenic patients compared with the unaffected siblings (p<0.05, 2-tailed, Table 3), while this difference only approached statistical significance in the comparison between schizophrenic patients and the healthy controls (p=0.115, 2-tailed, Table 3). Further comparison by two sample t-tests and paired t-tests of all the connectivities within the intrinsic networks validated the above findings, as the ANOVA results constituted a subset of the t-test results (Tables 4-6). These analyses also revealed increased anticorrelation between the schizophrenic patients and the healthy controls in the connection between the vMPFC and the R.DLPFC (p=0.045, Table 5) and between the schizophrenic patients and unaffected siblings in the connections between the vMPFC and the L.DLPFC (p=0.040, Table 6) and between the R.ITG and the R.IFG/R.Ins (p=0.017, Table 6).

Discussion

Abnormal connectivity in the intrinsic networks, the TNN and TPN, is increasingly hypothesized to play a role in schizophrenia pathophysiology [42, 61, 99-103]. To our knowledge, this is the first study to compare resting-state connectivity of both the TPN and TNN among schizophrenic patients, their unaffected siblings, and healthy controls. In the TNN, schizophrenic patients demonstrated hyperconnectivity between the PCC/PCu and left ITG and between the vMPFC and the right LPC, while both schizophrenic patients and their unaffected siblings exhibited hyperconnectivity between the bilateral ITG. In the TPN, schizophrenic patients showed hyperconnectivity between the left DLPFC and right IFG in comparison to unaffected siblings, although this abnormality only trended towards significance relative to healthy controls. An advantage of our methodology is that we examined connectivity throughout the intrinsic networks rather than focusing only on predefined regions of interest. Because we reconstructed the intrinsic networks in their entirety, we were able to examine the individual connectivities between each pair of regions in the networks. In addition, the overlap method enabled us to hone our connectivity analysis to precisely compare the same regions across the different subject groups and thereby avoid conflating differences in network composition with alterations in connectivity.

To situate the present study within the context of previous research on the intrinsic networks in schizophrenia, this study furthers the concept of distorted network connectivity in schizophrenia. Research to date, however, has produced conflicting results as to whether connectivity of the intrinsic networks is increased or decreased in schizophrenia. Our previous connectivity study of paranoid schizophrenic patients

identified hyperconnectivity of the TNN in the resting-state [42]. Other studies, however, demonstrated complex patterns of both increased and decreased connectivity in the TNN in schizophrenia [101, 102, 104, 105], while still others have primarily demonstrated decreased connectivity of the TNN in schizophrenia [100, 106]. In the TPN, we identified resting-state hyperconnectivity associated with schizophrenia in the current study, which is consistent with our previous work [42]. Studies of TPN connectivity in schizophrenia during task performance have demonstrated both increased connectivity [104] and decreased connectivity [107, 108] of the TPN. Finally, analysis of the anticorrelation between the TNN and the TPN has also produced uneven results. In this study, we did not identify any differences in anticorrelation among the schizophrenic patients, their unaffected siblings, and controls by ANOVA. In comparing the subject groups by t-tests, however, we found increased anticorrelation in schizophrenia relative to both the unaffected siblings and healthy controls. Previous studies have identified both increases [42, 102, 105] and decreases [103, 104] in anticorrelation associated with schizophrenia and thus a consensus has yet to develop. The inconsistency in schizophrenia connectivity results thus spans the TNN, TPN, and the anticorrelation between these networks. This variance may be attributed to the wide heterogeneity of both analysis methodologies and the illness itself. Analysis techniques in the studies above included independent component analysis [101, 102, 104-106], functional connectivity analysis based on specific regions of interest [100 105], and interregional functional connectivity analysis (our study), while the studies also varied between task performance and resting-state. While these different methods generally demonstrate the same core intrinsic networks, subtle differences in the composition of the identified networks may affect the connectivity analyses. Moreover, it is increasingly

apparent that the intrinsic anticorrelated networks are themselves composed of subnetworks [105, 109-111]. These subnetworks each have varying connectivity patterns with the remainder of the intrinsic networks [109], such that analysis at these individual levels may be necessary to produce a more nuanced view of the functional connectivity. Finally, the heterogeneity of schizophrenia in such aspects as illness subtype, medication status, and illness course, along with the small number of patients typically included in imaging studies [112] complicates these research studies.

Given the inconsistency to date of intrinsic network connectivity studies comparing schizophrenic patients to controls, it is hoped that the inclusion of patients' relatives will further elucidate the connectivity changes that are primary to schizophrenia and those associated with illness risk. There has been one other study that examined network connectivity in schizophrenic patients and their first-degree relatives and it also demonstrated shared TNN hyperconnectivity [103]. Furthermore, these abnormalities were present both during task-performance and in the resting-state and correlated with psychopathology and working memory deficits in the schizophrenic patients as well as their first-degree relatives [103]. Our current results are thus broadly consistent with those of Whitfield-Gabrieli *et al*., while we further show that hyperconnectivity in schizophrenia may extend to the TPN. Future research that includes the relatives of schizophrenic patients is advantageous in that these individuals share an increased genetic risk for the illness [113] while being free of confounds, such as antipsychotic use and institutionalization, associated with schizophrenic patients themselves. It is thus hoped that these unaffected relatives will both elucidate the primary processes of schizophrenia and improve our understanding of susceptibility to the illness.

Proper coordination and competition of cortical areas is crucial for optimal cognitive operations [28]. The TNN is associated with cognitive processes that focus primarily on the internal world, including self-monitoring and stimulus-independent thoughts, while maintaining baseline monitoring for unpredicted external stimuli [33, 43, 44]. Conversely, the TPN is involved in externally oriented, stimulus-driven attention and goal-directed cognitive processes [37, 38]. The coordination between the TNN and TPN can be understood as integration between internal information processing and engagement with the external world. Abnormal connectivity of the intrinsic networks in schizophrenic patients may compromise network function and aversely affect the transitions between these two networks such that the normally strong boundary between internal and external information processing may be blurred. For example, schizophrenic patients may have difficulty distinguishing self-generated speech from external voices, suggesting a mechanism for the generation of auditory hallucinations. Hyperconnectivity of the TNN may represent increased introspective thinking and heightened salience monitoring, such that external events are imbued with an inappropriate amount of self-relevance. Indeed, the correlation between psychopathology and aberrant activity and connectivity of the TNN has been repeatedly demonstrated in schizophrenic patients [100, 101, 103]. Furthermore, the importance of proper coordination between the intrinsic networks was highlighted by a study in which working memory performance (TPN activity) was inversely correlated with the frequency of intrusion of unrelated stimulus-independent thoughts (TNN activity) [60]. Our current findings of TNN and TPN hyperconnectivity are broadly consistent with our previous work [42] and further implicate disrupted network communication and competition in the symptoms of schizophrenia.

Interestingly, several of the regions identified as hyperconnected in this study underlie network coordination, the regulation of TNN and TPN activity. TNN hyperconnectivity in schizophrenic patients was identified between the PCC/PCu and left ITG and between the vMPFC and the right LPC. The PCC/PCu is postulated to regulate activity throughout the TNN as the key node of the network [38]. This role is based on the fact that the PCC/PCu is the most widely connected region in the TNN [33, 38], is metabolically more active than the other regions in the network [43], and has been implicated in numerous studies of internal information processing [114 115]. Previous studies of schizophrenia have repeatedly identified metabolic and activity abnormalities in the PCC/PCu [116-119]. Studies that have explicitly examined the PCC in the context of the TNN in schizophrenic patients have detected both hyper- and hypoconnectivity [100, 101, 103]. Moreover, this abnormal connectivity correlates with the symptoms of schizophrenia in both the resting-state [100] and during task performance [101, 103]. Thus, because the PCC/PCu is such an integral part of the TNN, abnormal connectivity of this region may compromise control and coordination of the entire network.

The MPFC has been designated the "second hub of the default network" [33] and along with the PCC forms the core of the TNN [37]. The MPFC is among the most metabolically active brain regions in the resting-state [29] and has widespread connections throughout the TNN [33]. Moreover, it has been linked to hypothesized functions of the TNN, such as the generation of stimulus independent thoughts [45] and self-relevant mental exploration [43]. A recent study employed Granger causality analyses to demonstrate that MPFC activity resulted in deactivation of a subset of the TPN, thus establishing a prominent role for the MPFC in network coordination [109]. Research in schizophrenia has revealed hyperactivity

of the MPFC [101, 112] along with volumetric decreases in this region [120]. A recent multimodal neuroimaging study of schizophrenia combined voxel based morphometry, functional imaging, and diffusion tensor imaging and identified the MPFC as the region with the most marked abnormalities across imaging techniques [121]. Our previous study of intrinsic network connectivity identified hyperconnectivity of the MPFC associated with schizophrenia [42]. Furthermore, hyperconnectivity of the MPFC was demonstrated during task performance and in the resting-state in both schizophrenic patients and their unaffected relatives [103], although there have also been reports of decreased MPFC connectivity in schizophrenia [100]. Finally, multiple studies have detected decreases in task-induced deactivations of the MPFC, indicating abnormal communication between the intrinsic networks [103, 122, 123]. Given its centrality to the TNN and its role in regulating activity of the TPN, altered connectivity of the MPFC has important implications for the coordination of the intrinsic networks.

TPN hyperconnectivity in schizophrenic patients was identified between the left DLPFC and the right IFG. While this difference was statistically significance in the comparison with unaffected siblings, there was only a trend towards significance in the comparison between schizophrenic patients and healthy controls. The right IFG is involved in cognitive control, the ability to orchestrate thoughts and actions in accordance with internal goals [124, 125]. A recent fMRI study analyzed signal changes in the right IFG and responses in the intrinsic networks and found a causal role for the right IFG in increasing TPN activity and decreasing TNN activity [126]. This role is further supported by the fact that the IFG is active in all phases of task control and therefore is postulated to form the core of the task regulatory system [127, 128]. The right IFG is critical

for the suppression of inappropriate impulses and actions [129, 130], and patients with lesions in the right IFG demonstrate difficulty in changing behavior in response to rule changes [131]. Thus, Sridharan *et al*. propose a model in which network switching is initiated in the right IFG, transmitted to the DLPFC, and then promulgated to the remainder of the TPN [126]. Furthermore, research in schizophrenic patients has demonstrated right IFG gray matter deficits [120, 132], white matter abnormalities [133] and abnormalities in functional connectivity [134]. Finally, psychotic symptoms, particularly auditory hallucinations, predominantly activate the right IFG [135, 136]. As a primary determinant of network switching and TPN activity, IFG connectivity has broad implications for coordination and activity throughout the TPN and TNN.

The DLPFC is one of the most widely connected regions in the TPN, enabling it to carry out network switching in concert with IFG signal induction. This role is particularly evident in the TPN driven central-executive system of working memory that allocates attention to different working memory modalities [33, 37, 137-139]. The DLPFC selectively activates and inhibits multiple working memory information sources, such as somatic, spatial, auditory, and visual processing areas [139] to modulate activity throughout the TPN. Working memory deficits are believed to be the core neuropsychological dysfunction in schizophrenia [140], and are hypothesized to contribute to the cognitive deficits and symptoms of schizophrenia [141, 142]. DLPFC abnormalities in schizophrenic patients have been detected in synaptic density, neural contents, gray matter density and volume, regional metabolism, and cerebral blood flow [143-148]. In addition, BOLD signal analysis of DLPFC connectivity within the TPN demonstrated hyperconnectivity in schizophrenia patients both during the resting-state [42] and during task performance [104]. Thus, much like

the PCC in the TNN, the IFG and the DLPFC are critical modulators of TPN activity and hyperconnectivity of these regions may affect the entirety of the TPN.

Both schizophrenic patients and their unaffected siblings demonstrated resting-state hyperconnectivity of the TNN between the bilateral ITG. Our finding is broadly consistent with a study by Whitfield-Gabrieli *et al*. in which TNN hyperconnectivity was shared by schizophrenic patients and their first-degree relatives [103]. This hyperconnectivity was evident both during the resting-state and during task performance and was correlated with working memory deficits [103]. In the current study, the specific TNN hyperconnectivity was between the bilateral ITG, which are involved in working memory and visual and language processing [149]. Multiple studies of the relatives of schizophrenia patients have identified deficits in the functions supported by the ITG and suggested that such cognitive impairments may be a phenotypic marker of the genetic loading for schizophrenia that these individuals carry [80, 81, 150, 151]. Furthermore, gray matter losses in the bilateral ITG have been reported in both schizophrenic patients [152, 153] and their non-psychotic siblings [154]. It is possible, therefore, that hyperconnectivity of the TNN underlies the cognitive deficits and increased risk for schizophrenia observed in the first-degree relatives of schizophrenic patients. The presence of TNN hyperconnectivity in the unaffected siblings suggests that this abnormality is a primary process associated with increased susceptibility to schizophrenia, rather than a secondary effect of the disease. Because few studies have examined the connectivity of the intrinsic network in the siblings of schizophrenic patients, future research is needed to further elucidate the precise regions and connectivities that are abnormal. Such work may ultimately contribute to developing schizophrenia endophenotypes that will both aid in identifying

individuals with the greatest illness risk and contribute to determining schizophrenia risk genes [75].

There are some methodological issues in this study that should be considered. First, despite the advantages to BOLD methodology, including the high spatiotemporal resolution it offers and the fact that it is non-invasive [155], there are some factors to consider with this technique. Physiologic factors that affect blood flow and oxygenation, such as the cardiac and respiratory cycles, may interfere with the BOLD signal [155, 156]. Given this signal distraction the relatively low sampling rate (TR=2s) for multi-slice acquisition in this study may have reduced the specificity of the connectivity effects [90]. Future studies may estimate, segregate, or remove these physiological effects by incorporating multivariate connectivity analysis methods, such as independent component analysis [157], which have been shown to be less vulnerable to physiologic confounders [158, 159]. Alternatively, or in addition, simultaneously recording the respiratory and cardiac cycles during data acquisition and including these as covariates could minimize the physiologic factors [160]. Despite the concern of physiologic confounders, however, some research indicates that low-frequency fluctuations are the major contributors to functional connectivity maps, with cardiac and respiratory cycles producing less than 10% of the effect [161].

The second limitation involves the overlap method used in this study in which only regions present in the intrinsic networks of all three of the subject groups were included in the connectivity analysis. Although the composition of the intrinsic networks was largely similar between the groups, the overlap method excluded regions that were not coincident across the three groups and it is possible that these regions have

pathophysiological implications for schizophrenia. Moreover, this exclusion meant that we did not address the variation in the spatial organization of the networks. This decision was made in order to focus precisely on the strength of the connectivity and avoid conflating differences in composition of the networks with variations in the strength of the interregional connections.

Finally, some heterogeneity in the schizophrenic patients existed with regard to illness subtype, antipsychotic use, and duration of illness, while nicotine use may have introduced variation across all subject groups. Although many of the patients in this study were in their first episode of schizophrenia, this was not true of every patient, nor did all patients share a schizophrenia subtype diagnosis. In addition, most of the schizophrenic patients in this study were receiving atypical antipsychotic medications at the time of scanning. While the effect of antipsychotic medications on the intrinsic networks is still unclear, some studies suggest these medications tend to normalize aberrant connectivity [9, 162]. Nicotine use was not an exclusion criterion in this study for any of the subject groups. Nicotine has been shown to increase neural activity and connectivity [163], and the nature of this influence may vary between schizophrenic patients and healthy controls [164]. Therefore, future studies may benefit from analyzing antipsychotic-naïve, first-episode patients who are non-smokers and carry a uniform schizophrenia subtype diagnosis. In addition, due to the small sample size in the current study, further research is needed to confirm the specific connectivity abnormalities identified by post hoc testing. As studies of this nature continue to proliferate, it is hoped that consensus will develop regarding the connectivity changes associated with schizophrenia.

Investigation of the resting-state connectivity of the anticorrelated intrinsic networks in schizophrenic patients and their unaffected siblings provides a unique opportunity to explore the pathophysiology of, and susceptibility to, schizophrenia. Hyperconnectivity of the TNN and TPN in schizophrenic patients may contribute to the symptoms and cognitive deficits observed in schizophrenia. Similar, but milder, TNN hyperconnectivity observed in the unaffected siblings of schizophrenic patients may contribute to their cognitive deficits and increased susceptibility to schizophrenia. Future studies based on a concept of distorted coordination of the intrinsic networks may improve our understanding of schizophrenia pathophysiology and susceptibility.

Figures

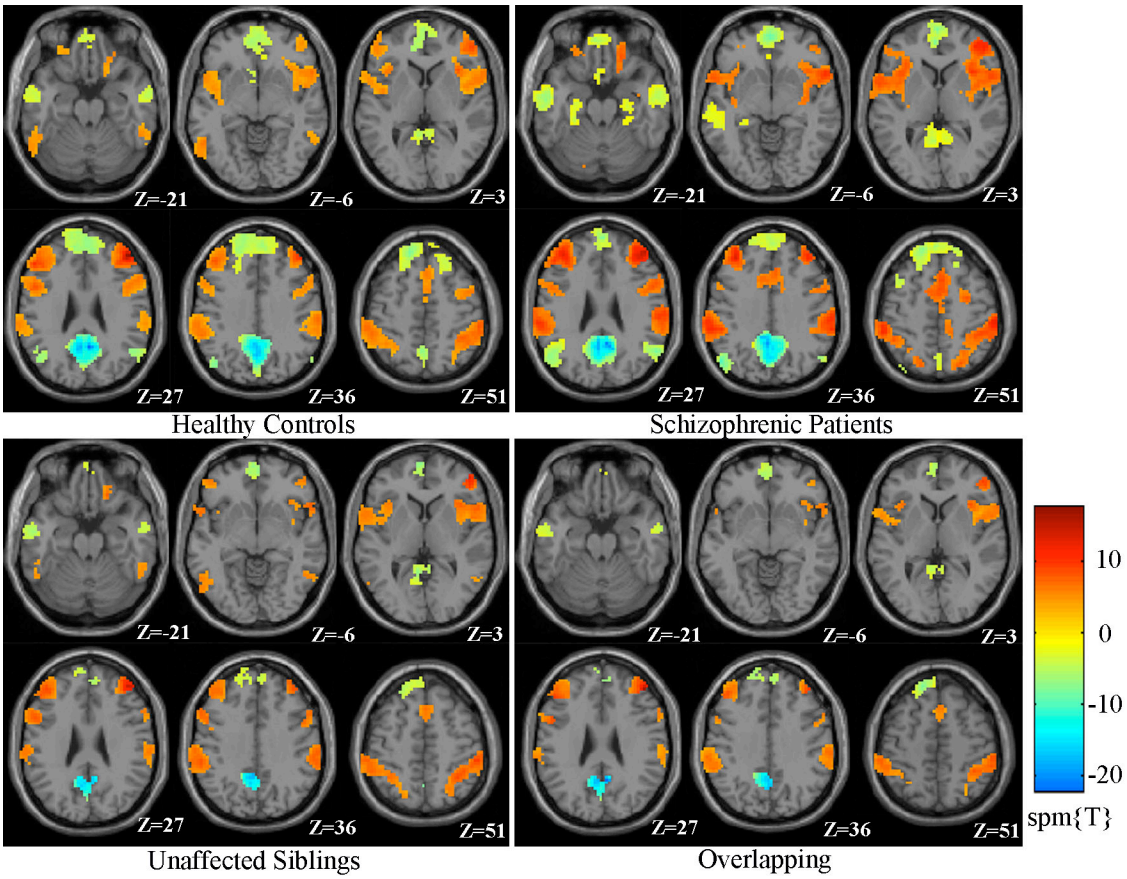

Figure 1. Intrinsic networks for each subject group and the overlapped intrinsic network among the three groups. The red-orange colors represent the regions of the task-positive network, while the light blue-yellow colors represent the regions of the task-negative network.

Tables

Table 1. Demographic and clinical profiles of the schizophrenic patients, unaffected siblings, and healthy controls (Mean±SD)

Characteristics		Schizophrenic Patients (n=25)	Unaffected Siblings (n=25)	Healthy Controls (n=25)
Age (year)		25.36±6.32	25.56±6.78	25.48±5.45
Education (year)		12.28±2.57	12.48±2.52	13.68±2.85
Sex (Male/Female)		13/12	15/10	14/11
Duration of illness (months)		18.32±15.84	-	-
PANSS	Total score	87.24±12.23	-	-
	Positive score	21.92±4.74	-	-
	Negative score	23.36±5.7	-	-
	General score	41.96±6.39	-	-

Table 2. The regions of the overlapped intrinsic organization across the three subject groups

Index	Region	Broadmann Area	Cluster Size (number of voxels)	MNI coordinates of peak voxels
Task-positive network				
1	L.DLPFC	9/10/46	299	-51 39 15
2	R.DLPFC	9/10/46	249	45 42 30
3	L.IFG/L.Ins	44/45/13/47	259	-51 9 24/-39 18 6
4	R.IFG/R.Ins	44/45/13/47	392	54 9 15/36 21 3
5	L.IPL	40/2	523	-60 -36 45
6	R.IPL	40/2	531	51 -39 57
7	R.dPM	6	16	33 0 63
8	SMA	8/6	52	3 24 51
9	R.OFC	11	17	21 30 -27
10	R.MT	21	6	60 -57 -9
Task-negative network				
11	PCC/PCu	23/31/7	363	6 -54 27
12	vMPFC	10/11	178	-6 51 15
13	L.dMPFC	8/9/10	211	-15 45 48
14	R.dMPFC	9/10	33	6 51 24
15	R.LPC	39/40	18	54 -60 27
16	L.ITG	20/21	82	-57 -3 -27
17	R.ITG	20/21	76	63 -6 -21

Abbreviations: L: left; R: right; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; Ins: insula; IPL: inferior parietal lobule; dPM: dorsal premotor area; SMA: supplementary motor area; OFG: orbital frontal gyrus; MT: middle temporal region; PCC: posterior cingulated cortex; PCu: precuneus; d/vMPFC: dorsal/ventral medial prefrontal cortex; LPC: lateral parietal cortex; ITG: inferior temporal gyrus.

Table 3. Differences in connectivity strength within the intrinsic organization between the three subject groups

Connectivity		HC: z value	SIB: z value	SCZ: z value	p value (post hoc tests)		
Region1	Region2	Mean±SD	Mean±SD	Mean±SD	HC vs. SIB	HC vs. SCZ	SIB vs. SCZ
Differences in the task-positive network							
L.DLPFC	R.IFG/R.Ins	0.36±0.21	0.31±0.22	0.47±0.24	0.355	0.115	0.014*
Differences in the task-negative network							
L.ITG	PCC/PCu	0.31±0.32	0.34±0.24	0.57±0.24	0.701	0.001**	0.003**
R.LPC	vMPFC	0.30±0.25	0.31±0.30	0.48±0.24	0.948	0.023*	0.027*
L.ITG	R.ITG	0.46±0.29	0.68±0.32	0.69±0.27	0.009**	0.006**	0.890
Differences between the networks							
None							

Notes: *p<0.05; **p<0.01.

Abbreviations: HC: healthy controls; SIB: unaffected siblings; SCZ: schizophrenic patients; L: left; R: right; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; Ins: insula; PCC: posterior cingulated cortex; PCu: precuneus; ITG: inferior temporal gyrus.

Table 4. Differences in connectivity strength within the intrinsic networks between the healthy controls and unaffected siblings

Connectivity		HC: z value	SIB: z value	P value*
Region1	Region2	Mean±SD	Mean±SD	
Differences in the task-positive network				
None				
Differences in the task-negative network				
L.ITG	R.ITG	0.46±0.29	0.68±0.32	0.013
Differences between the networks				
None				

* two sample t-test

Abbreviations: HC: healthy controls; SIB: unaffected siblings; L: left; R: right; ITG: inferior temporal gyrus.

Table 5. Differences in connectivity strength within the intrinsic networks between the healthy controls and schizophrenic patients

Connectivity		HC: z value	SCZ: z value	p value*
Region1	Region2	Mean±SD	Mean±SD	
Differences in the task-positive network				
R.dPM	R.OFG	0.04±0.17	0.14±0.20	0.046
Differences in the task-negative network				
L.ITG	PCC/PCu	0.31±0.32	0.57±0.24	0.002
R.LPC	vMPFC	0.30±0.25	0.48±0.24	0.016
L.ITG	vMPFC	0.24±0.25	0.42±0.32	0.026
L.ITG	L.dMPFC	0.37±0.20	0.53±0.34	0.047
L.ITG	R.ITG	0.46±0.29	0.69±0.27	0.005
Differences between the networks				
vMPFC	R.DLPFC	-0.27±0.26	-0.42±0.25	0.045

* two sample t-test

Abbreviations: HC: healthy controls; SCZ: schizophrenic patients; L: left; R: right; DLPFC: dorsolateral prefrontal cortex; PCC: posterior cingulated cortex; PCu: precuneus; ITG: inferior temporal gyrus; OFG: orbital frontal gyrus; d/vMPFC: dorsal/ventral medial prefrontal cortex; dPM: dorsal premotor area; LPC: lateral parietal cortex.

Table 6. Differences in connectivity strength within the intrinsic networks between the unaffected siblings (SIB) and the schizophrenic patients (SCZ)

Connectivity		SIB: z value	SCZ: z value	p value*
Region1	Region2	Mean±SD	Mean±SD	
Differences in the task-positive network				
R.IFG	L.DLPFC	0.31±0.22	0.47±0.24	0.024
SMA	L.IFG/L.Ins	0.24±0.29	0.40±0.21	0.039
R.MT	R.IPL	0.42±0.28	0.25±0.23	0.017
Differences in the task-negative network				
L.dMPFC	PCC/PCu	0.39±0.32	0.58±0.29	0.004
L.ITG	PCC/PCu	0.34±0.24	0.57±0.24	0.000
R.LPC	vMPFC	0.31±0.30	0.48±0.24	0.026
Differences between the networks				
L.dMPFC	L.DLPFC	-0.30±0.23	-0.45±0.24	0.040
L.ITG	R.IFG/R.Ins	-0.22±0.27	-0.39±0.27	0.017

* paired t-tests

Abbreviations: L: left; R: right; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; Ins: insula; IPL: inferior parietal lobule; dPM: dorsal premotor area; SMA: supplementary motor area; OFG: orbital frontal gyrus; MT: middle temporal region; PCC: posterior cingulated cortex; PCu: precuneus; d/vMPFC: dorsal/ventral medial prefrontal cortex; LPC: lateral parietal cortex; ITG: inferior temporal gyrus.

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