

Title: Network Trait marker for working memory deficit in Schizophrenia: a multi-site study

Abstract

Working memory impairment is documented as a core symptom related to cognitive deficits in schizophrenia. Understanding the pathology is very important to diagnosis and treatment of schizophrenia. While the working memory system is regarded as a complex one including both a central modality independent component and some slave modality specific storage buffer. The core regions mainly comprised the frontal-parietal areas known to be responsible for some higher-level procedures in working memory and have been evident to be impaired when the patients performing a working memory task. In this study, we attempt to find whether functional connectivity within the core working memory network is impaired at resting state. By recruiting a large scale multi-site resting-state fmri datasets, and performing a multi-site statistical analysis, we found that working memory deficits can be characterized by reduced functional connectivity among the caudal lateral prefrontal cortex, the left inferior frontal cortex, the left anterior insular and the right inferior parietal cortex. Association analysis of the impaired functional connectivity and clinical scores revealed no significant effect. Our findings indicate that the impaired resting-state functional connectivity within frontal-parietal core working memory network may act as a proxy of impaired top-down control in the working memory procedure, and thus lead to cognitive deficits in schizophrenia. The patterns of reduced connectivity provide stable trait marker for the disease and will help us to approach treatment.

Introduction

Working memory is conventionally defined as the ability to maintain and manipulate information over short periods. Working memory has been shown to be impaired in many neurological and psychiatric syndromes including Schizophrenia (Goldmanrakis, 1994; Silver et al., 2003). It was considered tightly associated with cognitive deficits in schizophrenia (Green et al., 2000). Examination of the underlying neurological mechanism provides us with insight into the causes, progression, and even treatment of schizophrenia. A large body of work incorporating neuroimaging tools such as functional magnetic resonance imaging (fMRI) has demonstrated that such patients have neurophysiological abnormality compared with the normal (Eryilmaz et al., 2016; Jansma et al., 2004; Shenton et al., 2001; Thermenos et al., 2005). Most of these studies focus on task related abnormal activation or connectivity when patients perform a working memory task. However, the results obtained under task may be perplexing due to several reasons. First, working memory is a complex system, which combines slavery components for encoding and maintaining of modality-specific short-term memory and central executive component to manipulate the information. Some studies have found both impairments in the modality-specific perception component and the manipulation component (Spindler et al., 1997). There has been evidence of multi-modality deficits in the working memory system including visual spatial, visual object, verbal, and other types of working memory (Glahn et al., 2001; Pae et al., 2008; Piskulic et al., 2007;

Shelley et al., 1995; Shelley et al., 1996). Second, a working memory task may incorporate several different procedures including maintenance, updating, retrieve etc. Activation or functional connectivity can be modulated by task configuration such as task load, stimulus type, task phase etc. In such condition, we can hardly make the conclusion about what fundamentally causes the impairment in the working memory system. Another concern is that working memory may be multidimensionally related to the psychosis (D'Esposito and Postle, 2015; Pukrop et al., 2003). The impairment may only present in certain group of the disease. Due to the heterogeneous configurations of tasks and the small sample sizes of the most imaging studies, previous findings of impairment during working memory task may be stage or modality dependent. Thus, it remains unsolved whether there exist some stable and fundamental deficits of working memory system in schizophrenia patients. In view of above-mentioned issues in previous studies, we applied the following strategy in our study.

We investigate the functional connectivity within the working memory network under resting state. Schizophrenia has often been conceived as a disorder of connectivity between components of large-scale brain networks (Jiang et al., 2013; Lynall et al., 2010). A growing number of studies have reported altered functional connectivity in schizophrenia during putatively “task-free” states and during the performance of cognitive tasks (Barch and Repovs, 2012; Zhou et al., 2007a; Zhou et al., 2007b). In comparison with task fMRI, resting state fMRI can be easily obtained and most importantly, it is independent of task configuration. Evidence has showed relation between the resting state signal and the working memory function. Recent study found

spontaneous low frequency fluctuations at rest in different areas were correlated with different modality based working memory measures (van Dam et al., 2015). Another study found the intrinsic anti-correlations between the medial prefrontal cortex (mPFC) and the dorsal lateral prefrontal cortex (dlPFC) measured by resting-state functional connectivity are related to behavioral measures of working memory capacity (Keller et al., 2015). Zou et al. (2013) found that resting-state activity could predict subsequent task-evoked brain responses and behavioral performance. All these proved the utility of resting-state fmri in research on working memory.

We restrict our analysis in a core network, which mainly comprise the fronto-parietal network including the pars opercularis part of inferior frontal gyrus (IFG), the anterior insula (AI), the pre-supplementary motor area (pre-SMA) and the intraparietal sulcus (IPS). This core network was identified by pooling various working memory tasks using quantitative coordinate-based meta-analysis over almost 200 individual experiments (Rottschy et al., 2012). The author draws attention to a consistent and restricted "core network" emerged from conjunctions across different types of working memory studies. This distributed network was believed to be active in working memory task ignoring the task type, stimulus type, and working memory load and may be act as a base part in working memory. By focusing on this core network, we expected to detect functional connectivity impairments in resting state, which may be a potential trait marker of working memory impairment in schizophrenia patients.

Most of the existing studies are limited by small sample sizes. To make our study powerful and reliable, we collect a large cohort of patients from six hospitals across

China. We applied a meta-analysis based strategy to pool results from single site and finally obtained statistically generalizable results.

stable trait biomarker across all task states.

A few studies have focused on the relationship between working memory impairment and disturbed functional connectivity both in the resting state and under various tasks. Some imaging studies reporting altered patterns of interregional functional connectivity in patients with schizophrenia during working memory task performance (Meyer-Lindenberg et al., 2001; Quintana et al., 2003; Schlosser et al., 2003a; Whalley et al., 2005). However, seldom studies have investigated the functional connectivity in resting state. Connectivity within the DMN and FP has been found significantly different between resting state and 0-back, and was further modulated by memory load. (Grega Repovs 2012)

There has been abundant imaging studies on WM deficits in Schizophrenia, but the differences among the tasks and material make it difficult to make a conclusion (consensus). Some studies have found evidence for different patterns of functional connectivity during different working memory task conditions (e.g., as a function of load, stimulus type, or task phase). Such findings suggest that functional connectivity changes could reflect differences in task engagement or responsivity of brain networks to modulation, rather than stable changes that persist across all task states. On the other hand, working memory itself is a complex system that consists of different components.

However, seldom researchers have pay attention to the abnormality of interaction within the WM network, which might occur to the resting state fmri of the patients. In this study, we assess the resting connectivity of core WM networks in a multi-site study framework. Such experiment configuration would help to find stable trait impairment in Schizophrenia, disregarding their age, sex, disease progress etc. (不对).

Results in these previous studies have been equivocal, and replication of experiment is needed.

Materials and Methods

Subjects

The resting state fMRI data presented here was collected from six hospitals in China that participated in the Brainnetome Project for Schizophrenia. The six hospitals are Peking University Sixth Hospital (PKUH6), Beijing Huilongguan Hospital (HLG), Xijing Hospital (XJ), Henan Mental Hospital (HM), Renmin Hospital of Wuhan University (RWU), and Zhumadian Psychiatric Hospital (ZMD). Henan Mental Hospital provided images from two distinct MRI scanners: Siemens (HMS) and General Electric (HMG). Patients and controls were matched for age, sex, handedness, and race distributions within each site. The local ethical review board approved the study at each center. All the participants provided written informed consent.

All schizophrenia patients (SZ) had a diagnosis of schizophrenia confirmed by trained psychiatrists using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P) (First, 2005). Exclusion criteria were a current neurologic disorder, a history of serious medical illness, substance dependence, pregnancy, electroconvulsive therapy within the last six months, or a diagnosis of any other Axis I disorder. The Positive and Negative Syndrome Scale (PANSS) was used to assess positive, negative, and general psychopathology symptoms in the patients (Kay et al., 1987). The healthy controls (HC), who had no current axis I psychiatric disorders, were recruited from the local community near each center through advertisements. None of the HCs had any personal history of psychotic illness and any family history of psychosis in their first, second, or third degree relatives. All the participants were Han Chinese in origin, right-handed, and had no contraindications to MRI scanning. After extensive quality checking of the brain imaging data, 446 SZs and 451 HCs were included in the analysis.

Data acquisition and preprocessing

Two types of 3T MRI scanners (four Siemens, three General Electric) were used at the participating centers (details in table \#). To ensure equivalent acquisition protocol and high quality imaging data, the scanning parameters of the functional scans at each of the six centers were set up by an experienced researcher before data acquisition. An echo planar imaging sequence was used to obtain the functional images, the parameters were as follows: 30 axial slices, TR = 2000 ms, TE = 30 ms, matrix = 64×64 , flip angle = 90° , FOV = $220 \times 220 \text{ mm}^2$, slice thickness = 4 mm, gap = 0.6 mm. 240 brain

volumes were collected, resulting in a total scan time of 480s. To be noticed, the time point number of the images from ZMD is 180 and is different from the 240 of the other sites. We did not exclude this site since we are eager to keep as much data and sites as possible, to support the validation of the multi-site analysis. The MRI scan sequences and parameters for each center are listed in eTable 1. The multi-site statistical strategy we used is robust to heterogynous data from different sites.

The images were preprocessed with an in-house software: Brainnetome Toolkit, which utilized Statistical Parametric Mapping SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). The first ten images were deleted for the signal equilibration. The remaining images were conducted for slice acquisition correction and head motion correction. The fMRI data which had less than 3.0 mm of head motion and 3.0° of angular rotation were included. There were no differences with regard to the maximum displacement and maximum rotation between groups, except that at HMS site SZs had higher maximum displacement (Wilcoxon rank sum test, $W = 2506.00$, $p < 0.02$, table #). Then the fMRI images were normalized to the standard Montreal Neurological Institute (MNI) template provided by SPM and resampled to the 3-mm isotropic voxels. Artefacts due to changes in global, ventricle and white matter signals, residual motion were removed using voxel-wise regression. A temporal filter ($0.01 \text{ Hz} < f < 0.08 \text{ Hz}$) were used to reduce the low-frequency drift and physiological high frequency respiratory and cardiac noise. Finally, the data was smoothed with an isotropic Gaussian kernel of 6 mm full-width at half-maximum.

Functional connectivity analysis

Regions of interest (ROIs)

The ROIs in this study were extracted from a previous meta-analysis (Rottschy et al., 2012), in which they found regions that commonly active during various working memory tasks. A consistent and restricted “core” network emerged from conjunctions across analyses of specific task designs and contrasts: task effects for n-back and Sternberg tasks, verbal and non-verbal tasks, load effects, and three task components (encoding, maintenance, recall). These regions include the pars opercularis part of IFG, the AI, the pre-SMA, and the IPS, bilaterally. The peak coordinates are listed in table \#. 5mm radius sphere ROIs were created from the peak coordinates in MNI standard space.

fcMRI Analyses

To perform the fcMRI analyses, time series from the resting-state scan were extracted by averaging the time series of all voxels in each ROI. The resulting time series of each ROI were then entered into the following connectivity analyses. The Pearson correlation coefficient was used to estimate functional connectivity between each pair of time series. A Fisher Z transform was applied to transform from Pearson r to z scores.

Statistical analysis

Group differences in the basic demographics at each center were examined with two-tailed t-tests and chi-square tests using R (R Core Team, 2015). For every single site separately, the diagnose effect on each FC value was assessed using a two-sample t-test comparing images between SZ and NC from each site. A second level random effects

meta-analysis was used to pooling the single site statistics, in order to assess the replication of the effects from the entire dataset. The meta-analysis was conducted in R with metafor packages (Viechtbauer, 2010). The effect sizes were calculated using Hedge's g , which provides an unbiased standardized mean difference that incorporates a correction for small sample sizes (Hedges and Olkin, 1985). Hedge's g was calculated using each center's means, standard deviations, and the corresponding sample size. The heterogeneity among studies (i.e., τ^2) was estimated with the DerSimonian-Laird estimator (DerSimonian and Laird, 1986; Raudenbush, 2009). Heterogeneity of the resulting mean-weighted effect sizes was tested with chi-square test. Variation in standardized mean difference (SMD) attributable to heterogeneity was measured by I^2 . Random-effect models were used for the meta-analyses when I^2 values exceeded 50%. All significance thresholds were set to false discovery rate FDR corrected $p < 0.001$ for multiple comparison.

We then examined the relationship between functional connectivities (FC) values of those that showed significant group effect previously and the clinical scores in patients including (PANSS positive, PANSS negative, PANSS general, and PANSS total). These analyses were conducted both separately with data from each site and with all the data. In whole data analysis, the site factor was included in the general linear model. An additional analysis was also performed with covariate of age and sex.

Results

Demographics and clinical data

Sociodemographic and psychopathological data are presented by center in Supplementary Tables. No statistically significant differences in age and sex were noted between the schizophrenia patients and HCs at each center. The patients had significantly fewer years of education than the HCs in five out of seven centers.

Group comparisons of FCs at each center

Random effect multicenter analysis

By applying the FDR corrected threshold, we found four reduced FCs in the patients compared to the normal group: they are the connection between the left IFG/caudal lateral prefrontal gyrus (SMD = and the left AI, the left IFG/caudal lateral prefrontal gyrus and the left IFG pars opercularis, the right IPS and the left IFG pars opercularis, the right IPS and the right IFG pars opercularis (Figure 1). No functional connectivity was detected with an enhanced effect in the patients group.

Association analysis

We did not find any association between the FCs and the clinical scores.

Discussion

Our results showed reduced resting-state functional connectivity from the caudal LPFC to the left AI and left IFG, pars opercularis. The LPFC is confirmed to be a core region responsible for higher-level representation or manipulation in working memory processes (D'Esposito and Postle, 2015). Meta-analysis finds evidence for the consistent activation of caudal LPFC across different putative executive functions (Nee

et al., 2013). The caudal LPFC also showed a working memory load-dependent effect in (Rottschy et al., 2012), whereas the rostral LPFC was not. This may indicate that the caudal LPFC was directly involved in manipulating the working memory storage. Earlier study showed the activation in caudal LPFC regions negatively correlated with the disorganization syndrome score of patients (Barbalat et al., 2009). Although these findings are under the context of cognition control, there might be similar effect in working memory because LPFC belong to a common network subserving a wide domain of cognitive tasks including working memory (Duncan and Owen, 2000). Our resting state results suggested that there might be dysfunction in the caudal LPFC, which may indicate functional impairment when processing working memory items. The impairment may propagate down to the other frontal areas in a hierarchical working memory network, as we found a reduced connectivity to the left AI and left IFG, two important regions involved in working memory. The inferior frontal gyrus/anterior insula (IFG/AI) was suggested to be involved in elaborate attentional and top-down control in adaption to working memory context, which help to prepare and update the strategies in working memory processing (Tops and Boksem, 2011). Ventral cortico-limbic control pathways that include the IFG/AI, may adapt to working memory context that differ in the level of predictability. Meta-analysis has find consistent activation in bilateral mid-ventrolateral prefrontal cortex (BA45, 47) within different N-back tasks, which suggested a modality independent involvement in working memory (Owen et al., 2005). Owen, Petrides and their colleagues [6,7] proposed that the mid-ventrolateral region (Brodmann's area [BA] 45/47) supports the organization of response sequences

based on information retrieved from posterior areas, whereas the mid-dorsolateral region (BA 9/46) supports the active manipulation or monitoring of information within working memory (Carpenter et al., 2000). Specifically, the inhibitory processes appear to be mediated by area 45 (left lateral prefrontal structures) (Jonides et al., 1998) in working memory tasks. Study find the left and right IFG showed a conjunction between working memory and inhibition tasks within subjects, which indicate some component of executive function may interactive with the working memory system in working memory tasks (McNab et al., 2008). The **right IFG** has been suggested to perform a general-purpose inhibitory function, and is related to inhibition of irrelevant memory from entering WM (Hampshire et al., 2010; Nee et al., 2013)(**Anderson et al. 2004; Anderson and Levy 2009, Nee, 2013**). One review gives attention to the role of AI in switching between other large-scale networks to facilitate access to attention and working memory resources when a salient event is detected (Menon and Uddin, 2010). Eriksson et al. (2015) reviewed that attention is understood to be a cornerstone of working-memory processed. When the perceptual input no longer is present, sustained attention along with a rehearsal process is crucial for maintaining the information in working memory. Individual differences in working memory capacity are also showed to be determined primarily by variability ability in attentional control deployment. In line with these existing findings, we suspect that the schizophrenia patients may lack the attention, the inhibition control ability to maintain, and manipulating the working memory items while not disturbed by unrelated staff. Moreover, there is evidence of structure abnormality of these areas in schizophrenia

patients. For example, the anterior insula is closely associated with working memory processes in healthy participants and shows gray matter reduction in schizophrenia (Clos et al., 2014). Cortical thinning in inferior frontal and insular is related to dysfunctional brain activation/deactivation during working memory task in schizophrenic patients (Pujol et al., 2013).

Apart from caudal LPFC, we also found connectivity reduction in the parietal lobe, i.e., from the IPS to bilateral IFG. The intraparietal sulcus (IPS) is a region known to be active during states of high attention to sensory stimulation or performance of attention-demanding tasks, as part of the attention control network, or task positive network. Evidence has showed it is anatomically organized in topographic maps of multisensory attention (Anderson et al., 2010). In a visual working memory task, the subjects' individual behavioral VWM capacity was predicted by neuronal synchrony in a network in which the IPS was the most central hub (Palva et al., 2010). With other hub areas like insula, cingulate and orbitofrontal structures formulating a cinguloopercular attention system that underlies the task set maintenance. Taken together, we suspect that the reduced connectivity between the IPS and bilateral IFG may indicate inefficiency in processing novel information in working memory.

Although there have been mounting evidence of altered LPFC connectivity with inferior parietal cortex, we did not detect a significant effect between the left caudal ROI and the IPS.

The frontal-parietal working memory core networks

The complex pattern of hyper-activation and hypo-activation found across studies implies that researchers should consider the entire network of regions involved in a given task when making inferences about the biological mechanisms of schizophrenia (Glahn et al., 2005). The organization of human WM has long been the topic of psychological models (Atkinson and Shiffrin, 1968), with maybe the most influential having been proposed by Baddeley and Hitch (1974). According to Baddeley and Hitch's model, the working memory system can be coarsely divided into a central executive module and some peripheral modality specific components. Working memory is the result of various combinations of processes; no processes (and correspondingly no brain structures) are unique or specific to working memory (Eriksson et al., 2015). **Many brain regions interact during working memory, including "executive" regions in the PFC, parietal cortex, and basal ganglia, as well as regions specialized for processing the particular representations to be maintained, such as the fusiform face area for maintaining face information.** Persistent neural activity in various brain regions accompanies working memory and is functionally necessary for maintenance and integration of information in working memory. Although there are different types of material modality, working memory task or contrast, large amount of previous related studies consistently find abnormality in the frontal-parietal network in patients. This network is well recognized as a core for higher order cognition such as

working memory and executive control (Duncan and Owen, 2000; Owen et al., 2005).

Our findings of the impaired functional connectivity are mainly located in a generic frontal-parietal network including the caudal LPFC, the left AI, the left IFG, and the right IPS. Previous studies of SZ patients when they perform WM tasks provide some evidence for impairment in this core network. A PET study has found impaired interaction between right lateral prefrontal cortex and bilateral inferior parietal region in SZ patients compared with normal patients during working memory processing (Kim et al., 2003). A study confirmed decreased connectivity between R_IPL and R_VLPFC, which connection was associated with the task score/performance in visuospatial n-back task (Quide et al., 2013). Tan et al. (2007) find a compensation role of ventral prefrontal areas to the dorsal prefrontal areas with the increase of working memory load in the high-and low-performing patient groups. They also find relatively greater connectivity between ventral prefrontal cortex and PPC in patients while comparison subjects had greater functional connectivity between the dorsal prefrontal cortex and posterior parietal cortex. Recently, a coordinate based meta analyses confirmed that MFG(BA9), rIFG(BA44) showed decrease in neural activation of schizophrenia unaffected relatives while right frontopolar (BA10), and left IPL(BA40) and bilaterally thalamus showed increased activation , both during working memory tasks (Zhang et al., 2016). There are some evidence about the structure deficits in IFG and insular in relation to dysfunctional brain activation/deactivation during working memory task in schizophrenia patients (Nuria Pujol, 2013). In this confirmatory study, we verified several reduced connectivity within the prefrontal-parietal network.

Neurodevelopmental model supposes in schizophrenia the presence of “silent lesion” in the brain, mostly in the parts, important for the development of integration (frontal, parietal and temporal), which is caused by different factors (genetic, inborn, infection, trauma...) during very early development of the brain in prenatal or early postnatal period of life.

Resting state and working memory

The ability to predict task performance with resting state data is unproven. A few studies investigate the relationship between resting state signal and task state signal. In Hampson et al. (2006), they found performance on the working memory task was positively correlated with the strength of functional connection between two regions within the default mode network both during the working memory and at rest. This study raise the possibility that the individual differences in coupling strength at rest predict differences in cognitive abilities important for this working memory task. Another study showed fractional amplitude of low frequency fluctuations (fALFF) at rest is correlated with domain and demand-specific working memory performance (van Dam et al., 2015). The other study found that smaller amplitudes of low-frequency BOLD oscillations during rest, measured by fALFF, were significantly associated with poorer cognitive performance, sometimes similarly in both groups and sometimes only in SZ, in regions known to subserve sustained attention and working memory. Some other studies provide evidence for a correlation between working memory performance

and functional network integration on different levels of network organization (Alavash et al., 2015). Taken together, these data suggest that the magnitude of resting-state BOLD oscillations shows promise as a biomarker of cognitive function in health and disease (Fryer et al., 2015).

There have been studies showing structure deficits associated with working memory performance, which indicated that both task impairment and dysconnection in rest might have common bases in structure.

Multi-site analysis

As we considered, the scanner, imaging protocol and clinical measures may bias a single site imaging study. To overcome these drawbacks, we acquired high quality fMRI data with common protocol from hospitals distributed across China. The subjects are also recruited under the same criteria and the clinical scores are assessed according to the standard. Despite these controlled measures, the data and the statistical results may be influenced by the differences in psychopathology, exposure to antipsychotic medication, scanner type and some other potential effects from different sites. In order to assess the generalization of the effects, meta-analysis is used here to pooling results from single site to increase the statistical power (Costafreda, 2009; Turner et al., 2013). To model the heterogeneous induced by the different subjective groups, acquisition software and hardware, and the individual variance in coregistering to the template, we introduced site factor as a random effect. By applying such multi-site experiment design and pooling strategy, we were able to, first, reduce the possibility of biased results in a

single site, and provide more reliable and generalized results; second, extract novel insights from existing large-scale datasets by increasing the statistical power. Variation caused by confounding effect can be covered by the large sample size; the results may generalize over sites and are more likely to be substantial.

Limitations

The present findings must be considered with respect to several limitations.

Some researchers suspect that working memory is a distributed system rather than represented in a few isolated core areas (Eriksson et al., 2015). Evidence showed that schizophrenia patients have diffuse impairment across brain (Buckley, 2005; Fioravanti et al., 2012; Jiang et al., 2013). This phenomena leads to the possibility that the impairment in WM networks could be also distributed across the WM networks. This may explain the difficulty in finding consistent results in imaging research. The poor behavior performance of patients may be composite of weak effect of different regions within the networks. Some studies focus on whole brain network properties such as the global clustering index etc 文献. Such kind of studies is limitless in helping to understand a specific dimension (WM) in the disease. The advantage of our design is it focuses on the core regions in WM network in related to most symptoms in schizophrenia. Nevertheless, this may lack the specificity when explaining symptoms caused by some modality specific impairment even in the working memory tasks. It cannot give us the knowledge how the higher order networks interact with lower level

regions during the working memory tasks. (再加点)

2. We did not find any association between these impaired functional connectivity with PANSS scores (PANSS total, PANSS general, PANSS negative and PANSS positive). One reason is that schizophrenia is a multi-dimensional disease and these scores does not reflect one spectral of impairment like working memory but is a combination of different deficits. Another reason is that the association may be too weak to detect. As pointed in Duncan and Owen (2000), the frontal-parietal networks are comprised of core regions, which may involve in multiple cognitive procedures. Because we did not detect the direct association of imaging finding to behavior, we are not sure whether these impairments are also related to other behavior domain. 补充

Conclusion

In conclusion, our investigation provides evidence for working memory resting-state function network impairment in schizophrenia, mainly involving the functional connectivity in the frontal-parietal network. Our findings are draw from a large-scale multi-site study with subjects collected from seven hospitals in China which lead to powerful and reliable conclusion that the working memory deficits are mainly ascribed to the dysfunction of high-level nodes comprises the “core” working memory network. The results may informed us the causes of this disease and facilitating future study on the pathology and treatment of this disease.

Funding/Support:

This work was supported in part by the National Key Basic Research and Development

Program (973) (Grant 2011CB707800), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB02030300).

Role of the Funder/Sponsor:

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions:

References

- Alavash, M., Doebl, P., Holling, H., Thiel, C.M., Giessing, C., 2015. Is functional integration of resting state brain networks an unspecific biomarker for working memory performance? *Neuroimage* 108, 182-193.
- Anderson, J.S., Ferguson, M.A., Lopez-Larson, M., Yurgelun-Todd, D., 2010. Topographic maps of multisensory attention. *Proc Natl Acad Sci U S A* 107, 20110-20114.
- Atkinson, R.C., Shiffrin, R.M., 1968. Human memory: A proposed system and its control processes. *Psychology of learning and motivation* 2, 89-195.
- Baddeley, A.D., Hitch, G., 1974. Working memory. *Psychology of learning and motivation* 8, 47-89.

Barbalat, G., Chambon, V., Franck, N., Koechlin, E., Farrer, C., 2009. Organization of cognitive control within the lateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 66, 377-386.

Barch, D.M., Repovs, G., 2012. Working Memory Related Brain Network Connectivity in Individuals with Schizophrenia and Their Siblings. *Psychophysiology* 49, S4-S4.

Buckley, P.F., 2005. Neuroimaging of schizophrenia: structural abnormalities and pathophysiological implications. *Neuropsychiatr Dis Treat* 1, 193-204.

Carpenter, P.A., Just, M.A., Reichle, E.D., 2000. Working memory and executive function: evidence from neuroimaging. *Curr Opin Neurobiol* 10, 195-199.

Clos, M., Rottschy, C., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2014. Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. *Neuroimage* 99, 269-280.

Costafreda, S.G., 2009. Pooling FMRI data: meta-analysis, mega-analysis and multi-center studies. *Front Neuroinform* 3, 33.

D'Esposito, M., Postle, B.R., 2015. The cognitive neuroscience of working memory. *Annu Rev Psychol* 66, 115-142.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control Clin Trials* 7, 177-188.

Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 23, 475-483.

Eriksson, J., Vogel, E.K., Lansner, A., Bergstrom, F., Nyberg, L., 2015. Neurocognitive Architecture of Working Memory. *Neuron* 88, 33-46.

Eryilmaz, H., Tanner, A.S., Ho, N.F., Nitenson, A.Z., Silverstein, N.J., Petrucci, L.J., Goff, D.C., Manoach, D.S., Roffman, J.L., 2016. Disrupted Working Memory Circuitry in Schizophrenia: Disentangling fMRI Markers of Core Pathology vs Other Aspects of Impaired Performance. *Neuropsychopharmacology*.

Fioravanti, M., Bianchi, V., Cinti, M.E., 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. *BMC Psychiatry* 12.

First, M.B., 2005. Structured clinical interview for DSM-IV-TR Axis I disorders: Patient edition. Biometrics Research Department, Columbia University.

Fryer, S.L., Roach, B.J., Ford, J.M., Turner, J.A., van Erp, T.G., Voyvodic, J., Preda, A., Belger, A., Bustillo, J., O'Leary, D., Mueller, B.A., Lim, K.O., McEwen, S.C., Calhoun, V.D., Diaz, M., Glover, G., Greve, D., Wible, C.G., Vaidya, J., Potkin, S.G., Fbirn, Mathalon, D.H., 2015. Relating Intrinsic Low Frequency Bold Cortical Oscillations to Cognition in Schizophrenia. *Neuropsychopharmacology*.

Glahn, D.C., Poutanen, V., Therman, S., Huttunen, M.O., Lonnqvist, J., Standertskjold-Nordenstam, C., Cannon, T.D., 2001. Neural correlates of spatial working memory dysfunction in schizophrenia. *Schizophr Res* 49, 176-177.

Glahn, D.C., Ragland, J.D., Abramoff, A., Barrett, J., Laird, A.R., Bearden, C.E., Velligan, D.I., 2005. Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp* 25, 60-69.

Goldman-Rakic, P.S., 1994. Working-Memory Dysfunction in Schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences* 6, 348-357.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* 26, 119-136.

Hampshire, A., Chamberlain, S.R., Monti, M.M., Duncan, J., Owen, A.M., 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* 50, 1313-1319.

Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T., 2006. Brain connectivity related to working memory performance. *J Neurosci* 26, 13338-13343.

Hedges, L., Olkin, I., 1985. *Statistical models for meta-analysis*. New York: Academic Press.

Hedges, LV, & Pigott, TD (2001). The power of statistical tests in meta-analysis. *Psychological Methods* 6, 203-217.

Jansma, J.M., Ramsey, N.F., van der Wee, N.J., Kahn, R.S., 2004. Working memory capacity in schizophrenia: a parametric fMRI study. *Schizophr Res* 68, 159-171.

Jiang, T., Zhou, Y., Liu, B., Liu, Y., Song, M., 2013. Brainnetome-wide association studies in schizophrenia: the advances and future. *Neurosci Biobehav Rev* 37, 2818-2835.

Jonides, J., Smith, E.E., Marshuetz, C., Koeppe, R.A., Reuter-Lorenz, P.A., 1998. Inhibition in verbal working memory revealed by brain activation. *Proc Natl Acad Sci U S A* 95, 8410-8413.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13, 261-276.

Keller, J.B., Hedden, T., Thompson, T.W., Anteraper, S.A., Gabrieli, J.D., Whitfield-Gabrieli, S., 2015. Resting-state anticorrelations between medial and lateral prefrontal cortex: association with working memory, aging, and individual differences. *Cortex* 64, 271-280.

Kim, J.J., Kwon, J.S., Park, H.J., Youn, T., Kang, D.H., Kim, M.S., Lee, D.S., Lee, M.C., 2003. Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia: A [O-15]H₂O PET study. *American Journal of Psychiatry* 160, 919-923.

Lynall, M.E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., Muller, U., Bullmore, E., 2010. Functional connectivity and brain networks in schizophrenia. *J Neurosci* 30, 9477-9487.

McNab, F., Leroux, G., Strand, F., Thorell, L., Bergman, S., Klingberg, T., 2008. Common and unique components of inhibition and working memory: an fMRI, within-subjects investigation. *Neuropsychologia* 46, 2668-2682.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function* 214, 655-667.

Nee, D.E., Brown, J.W., Askren, M.K., Berman, M.G., Demiralp, E., Krawitz, A., Jonides, J., 2013. A meta-analysis of executive components of working memory. *Cereb Cortex* 23, 264-282.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 25, 46-59.

Pae, C.U., Juh, R., Yoo, S.S., Choi, B.G., Lim, H.K., Lee, C., Paik, I.H., Jeun, S.S., Lee, C.U., 2008. Verbal working memory dysfunction in schizophrenia: An fMRI investigation. *International Journal of Neuroscience* 118, 1467-1487.

Palva, J.M., Monto, S., Kulashekhar, S., Palva, S., 2010. Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proc Natl Acad Sci U S A* 107, 7580-7585.

Piskulic, D., Olver, J.S., Norman, T.R., Maruff, P., 2007. Behavioural studies of spatial working memory dysfunction in schizophrenia: A quantitative literature review. *Psychiatry Res* 150, 111-121.

Pujol, N., Penades, R., Rametti, G., Catalan, R., Vidal-Pineiro, D., Palacios, E., Bargallo, N., Bernardo, M., Junque, C., 2013. Inferior frontal and insular cortical thinning is related to dysfunctional brain activation/deactivation during working memory task in schizophrenic patients. *Psychiatry Res* 214, 94-101.

Pukrop, R., Matuschek, E., Ruhrmann, S., Brockhaus-Dumke, A., Tendolkar, I., Bertsch, A., Klosterkotter, J., 2003. Dimensions of working memory dysfunction in schizophrenia. *Schizophr Res* 62, 259-268.

- Quide, Y., Morris, R.W., Shepherd, A.M., Rowland, J.E., Green, M.J., 2013. Task-related fronto-striatal functional connectivity during working memory performance in schizophrenia. *Schizophr Res* 150, 468-475.
- R Core Team, 2015. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>.
- Raudenbush, S.W., 2009. Analyzing effect sizes: Random-effects models. *The handbook of research synthesis and meta-analysis* 2, 295-316.
- Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A.R., Schulz, J.B., Fox, P.T., Eickhoff, S.B., 2012. Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage* 60, 830-846.
- Shelley, A.M., Grochowski, S., Lieberman, J.A., Javitt, D.C., 1995. Visual Working-Memory Dysfunction and P3 in Schizophrenia. *Schizophr Res* 15, 185-185.
- Shelley, A.M., Javitt, D.C., Vaughan, H.G., 1996. Mechanisms of auditory working memory dysfunction in schizophrenia. *Biol Psychiatry* 39, 526-526.
- Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. *Schizophr Res* 49, 1-52.
- Silver, H., Feldman, P., Bilker, W., Gur, R.C., 2003. Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry* 160, 1809-1816.
- Spindler, K.A., Sullivan, E.V., Menon, V., Lim, K.O., Pfefferbaum, A., 1997. Working memory deficits in schizophrenia: Dysfunction in multiple systems, not in the central executive. *Schizophr Res* 24, 137-137.
- Tan, H.Y., Callicott, J.H., Weinberger, D.R., 2007. Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex* 17 Suppl 1, i171-181.
- Thermenos, H.W., Goldstein, J.M., Buka, S.L., Poldrack, R.A., Koch, J.K., Tsuang, M.T., Seidman, L.J., 2005. The effect of working memory performance on functional MRI in schizophrenia. *Schizophr Res* 74, 179-194.
- Tops, M., Boksem, M.A., 2011. A potential role of the inferior frontal gyrus and anterior insula in cognitive control, brain rhythms, and event-related potentials. *Front Psychol* 2, 330.
- Turner, J.A., Damaraju, E., van Erp, T.M., Mathalon, D.H., Ford, J.M., Voyvodic, J., Mueller, B.A., Belger, A., Bustillo, J., McEwen, S., Potkin, S.G., Calhoun, V.D., Fbirt, 2013. A multi-site resting state fMRI study on the amplitude of low frequency fluctuations in schizophrenia. *Front Neurosci* 7.
- van Dam, W.O., Decker, S.L., Durbin, J.S., Vendemia, J.M., Desai, R.H., 2015. Resting state signatures of domain and demand-specific working memory performance. *Neuroimage* 118, 174-182.
- Viechtbauer, W., 2010. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software* 36, 1-48.
- Zhang, R., Picchioni, M., Allen, P., Touloupoulou, T., 2016. Working Memory in Unaffected Relatives of Patients with Schizophrenia: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies. *Schizophr Bull*.
- Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z., Liu, H., Kuang, F., 2007a. Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. *Neurosci Lett* 417, 297-302.
- Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2007b. Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophr Res* 97, 194-205.
- Zou, Q., Ross, T.J., Gu, H., Geng, X., Zuo, X.N., Hong, L.E., Gao, J.H., Stein, E.A., Zang, Y.F., Yang,

Y., 2013. Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Hum Brain Mapp* 34, 3204-3215.

	Maximum displacement		Maximum rotation	
	Test Statistics	p	Test Statistics	p
HLG	1860.50	0.70	1826.00	0.84
PKUH6	2953.00	0.40	2752.00	0.13
WUHAN	2552.50	0.92	2898.50	0.20
HMG	1371.00	0.77	1494.00	0.64
HMS	2506.00	0.02	2953.00	0.40
ZMD	1523.00	0.46	1357.00	0.77
XJ	1215.00	0.69	1133.00	0.85

Scanning sequences and parameters used at each center

	Center	PKUH6/HLG/XJ	HMS	HMG	RWU	ZMD
MRI scanner type	Vendor	Siemens	Siemens	General Electric	General Electric	General Electric
	Model	TrioTim 3T	Verio 3T	Signa HDx 3T	Signa HDxt 3T	Signa HDxt 3T
MRI scan sequence and parameters	Sequence	BOLD fMRI	BOLD fMRI	BOLD fMRI	BOLD fMRI	BOLD fMRI
	TR (ms)	2000	2000	2000	2000	2000
	TE (ms)	30	30	30	30	30
	Scan time (s)	480	480	480	480	360
	Number of Slices	33	33	33	33	33
	FA (°)	90	90	90	90	90
	Orientation	Axial	Axial	Axial	Axial	Axial
	Matrix size	64*64	64*64	64*64	64*64	64*64
	Pixel Spacing	3.44*3.44	3.44*3.44	3.44*3.44	3.44*3.44	3.44*3.44
	FOV(mm ²)	220*220	220*220	220*220	220*220	220*220
	Slice Thickness (mm)	4	4	4	4	4
	Gap (mm)	0.6	0.6	0.6	0.6	0.6

Table #. Demographic and Clinical Information (HLG).

HLG Site (3.0T Siemens TrioTim)	HC (n = 55)	SZ (n = 65)	Test Statistics	<i>p</i>
Age (Years)	24.89 (5.37)	26.06 (5.38)	$T = -1.19$	0.24
Gender (M/F)	26/29	26/39	$\chi^2 = 0.38$	0.54
Handedness(right/left)				
Education (Years)	13.33 (4.59)	13.33 (3.05)	$T = 0.75$	0.45
Duration of illness (Months)	NA	60.79 (49.78)	NA	NA
PANSS total	NA	79.00 (6.71)	NA	NA
PANSS positive	NA	26.25 (2.94)	NA	NA
PANSS negative	NA	16.69 (3.37)	NA	NA
PANSS general	NA	36.06 (3.85)	NA	NA

Age, handedness, and education data represent mean (SD). M: male; F, female.

Table #. Demographic and Clinical Information (PKUH6).

PKUH6 Site (3.0T Siemens TrioTim)	HC (n = 80)	SZ (n = 80)	Test Statistics	<i>p</i>
Age (Years)	25.83 (5.44)	27.32 (6.73)	$T = -1.54$	0.13
Gender (M/F)	46/34	50/30	$\chi^2 = 0.23$	0.63
Handedness(right/left)				
Education (Years)	13.61 (3.53)	13.26 (3.59)	$T = 0.63$	0.53
Duration of illness (Months)	NA	45.88 (53.53)	NA	NA
PANSS total	NA	77.92 (9.31)	NA	NA
PANSS positive	NA	23.84 (4.10)	NA	NA
PANSS negative	NA	18.26 (5.72)	NA	NA
PANSS general	NA	35.83 (5.35)	NA	NA

Table #. Demographic and Clinical Information (WUHAN).

WUHAN Site (3.0T Signa HDx 3T)	HC (n = 77)	SZ (n = 67)	Test Statistics	<i>p</i>
Age (Years)	24.89 (5.37)	26.06 (5.38)	$T = -1.03$	0.30
Gender (M/F)	37/40	28/39	$\chi^2 = 0.34$	0.59
Handedness(right/left)				
Education (Years)	14.60 (2.24)	11.76 (3.55)	$T = 5.61$	$P < 0.00$
Duration of illness (Months)	NA	42.82 (37.09)	NA	NA
PANSS total	NA	88.04 (12.08)	NA	NA
PANSS positive	NA	23.69 (4.21)	NA	NA
PANSS negative	NA	21.18 (6.04)	NA	NA
PANSS general	NA	43.18 (7.65)	NA	NA

Table #. Demographic and Clinical Information (HMG)

HMG Site (3.0T Signa HDx 3T)	HC (n = 66)	SZ (n = 43)	Test Statistics	<i>p</i>
Age (Years)	30.75 (7.28)	29.24 (7.81)	$T = 1.01$	0.31
Gender (M/F)	32/34	24/19	$\chi^2 = 0.30$	0.58
Handedness(right/left)				
Education (Years)	13.08 (4.51)	9.14 (3.42)	$T = 5.17$	0.00
Duration of illness (Months)	NA	51.00 (62.52)	NA	NA
PANSS total	NA	88.70 (11.91)	NA	NA
PANSS positive	NA	24.44 (3.65)	NA	NA
PANSS negative	NA	23.60 (5.57)	NA	NA
PANSS general	NA	40.65 (6.55)	NA	NA

Table #. Demographic and Clinical Information (HMS)

HMS Site (3.0T Siemens Verio 3T)	HC (n = 80)	SZ (n = 80)	Test Statistics	<i>p</i>
Age (Years)	27.16 (5.70)	26.09 (5.36)	$T = 1.23$	0.22
Gender (M/F)	42/38	43/37	$\chi^2 = 0.00$	1.00
Handedness(right/left)				
Education (Years)	13.82 (2.85)	11.13 (2.83)	$T = 5.96$	<0.00
Duration of illness (Months)	NA	39.92 (38.80)	NA	NA
PANSS total	NA	81.12 (8.52)	NA	NA
PANSS positive	NA	22.54 (2.80)	NA	NA
PANSS negative	NA	19.52 (5.33)	NA	NA
PANSS general	NA	39.06 (5.46)	NA	NA

Table #. Demographic and Clinical Information (ZMD).

ZMD Site (3.0T Signa HDx 3T)	HC (n = 53)	SZ (n = 53)	Test Statistics	<i>p</i>
Age (Years)	33.29 (7.09)	31.03 (7.38)	$T = 1.61$	0.11
Gender (M/F)	24/29	26/27	$\chi^2 = 0.04$	0.85
Handedness(right/left)				
Education (Years)	12.87 (3.31)	8.71 (3.60)	$T = 6.16$	<0.00
Duration of illness (Months)	NA	64.95 (64.14)	NA	NA
PANSS total	NA	87.47 (13.67)	NA	NA
PANSS positive	NA	25.43 (5.09)	NA	NA
PANSS negative	NA	21.04 (5.76)	NA	NA
PANSS general	NA	41.00 (6.40)	NA	NA

Table #. Demographic and Clinical Information (XJ).

XJ Site (3.0T Siemens TrioTim)	HC (n = 40)	SZ (n = 58)	Test Statistics	<i>p</i>
Age (Years)	29.74 (6.36)	27.54 (5.95)	$T = 1.73$	0.09
Gender (M/F)	21/19	30/28	$\chi^2 = 0.00$	1.00
Handedness(right/left)				
Education (Years)	13.00 (3.19)	10.05 (4.81)	$T = 3.65$	<0.00
Duration of illness (Months)	NA	25.98 (29.78)	NA	NA
PANSS total	NA	88.95 (14.07)	NA	NA
PANSS positive	NA	22.34 (4.91)	NA	NA
PANSS negative	NA	22.31 (5.73)	NA	NA
PANSS general	NA	44.29 (8.02)	NA	NA

HLG Site	HC	SZ	Statistics
3.0T Siemens TrioTim	(n =)	(n=)	
Age(mean,sd)	24.89 (5.37)	26.06 (5.38)	T=-1.19, p=0.24
Gender(male/female)	26/29	26/39	$\chi^2 = 0.38$, p = 0.54
Handeness(right/left)			
Mean years of education (SD)	13.33 (4.59)	13.33 (3.05)	T=0.75,p=0.45
Mean months of illness duration (SD)	NA	60.79 (49.78)	NA
PANSS total (SD)	NA	79.00 (6.71)	NA
PANSS positive (SD)	NA	26.25 (2.94)	NA
PANSS negative (SD)	NA	16.69 (3.37)	NA
PANSS hallucination (SD)	NA	36.06 (3.85)	NA

	PANSS total		PANSS positive		PANSS negative		PANSS general	
	r	p	r	p	r	p	r	p
HLG								
PKUH6								
WUHAN								
HMG								
HMS								
ZMD								
XJ								
ALL	0.08	0.11	0.07	0.13	0.04	0.44	0.05	0.31

	PANSS total		PANSS positive		PANSS negative		PANSS general	
	r	p	r	p	r	p	r	p
HLG								
PKUH6								
WUHAN								
HMG								
HMS								
ZMD								
XJ								
ALL	0.08	0.11	0.07	0.13	0.04	0.44	0.05	0.31

Table#. Association of FC1 and clinical scores in patients.

	PANSS total		PANSS positive		PANSS negative		PANSS general	
	r	p	r	p	r	p	r	p
HLG								
PKUH6								
WUHAN								
HMG								
HMS								
ZMD								
XJ								
ALL	0.08	0.11	0.07	0.13	0.04	0.44	0.05	0.31

Figure 1.

Four reduced functional connectivities (left cIFG – left AI; left cIFG – left IFG_oper; left IFG_oper – right IPS; right IFG_oper – right IPS). The pooled effect sizes were represented with different colors of the edges, lower value in the color bar means more reduced connection in the SZs compared with the HCs.

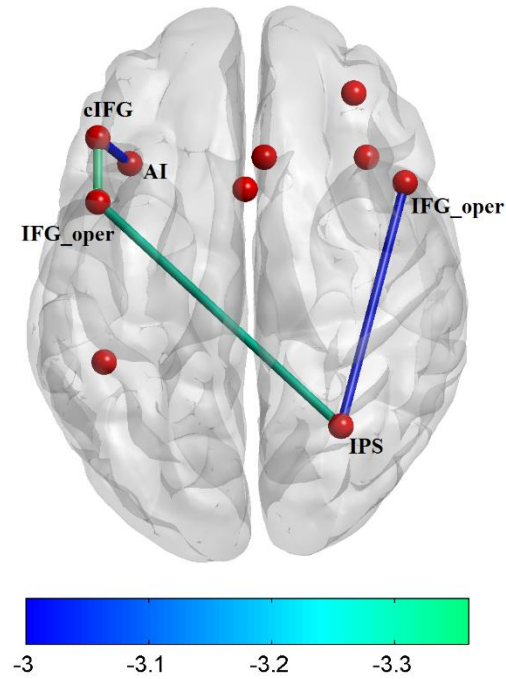


Figure 3.

Forest plot for studies of FC2 from all the sites, with standard mean difference (SMD) as outcome.

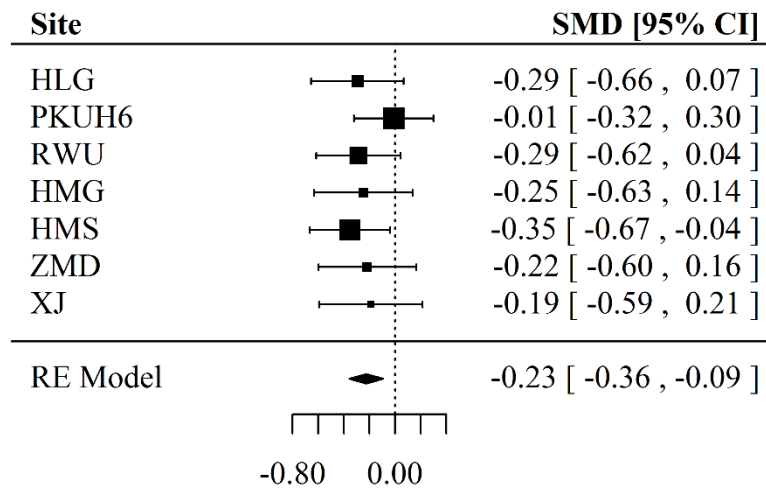


Figure 2.

Forest plot for studies of FC1 from all the sites, with standard mean difference (SMD) as outcome. Each study is shown with its 95% confidence interval CI. The size of the square symbol is proportional to the weight assigned to the study in the pooled estimate using a random effects model. Test of heterogeneity result is shown in text below the plot. Q is the chi-squared statistic and df is its degrees of freedom. I^2 is the percentage of variation in standardized mean difference (SMD) attributable to heterogeneity. The DerSimonian and Laird estimate of the pooled effect size is reported together with the 95% confidence interval in square brackets.

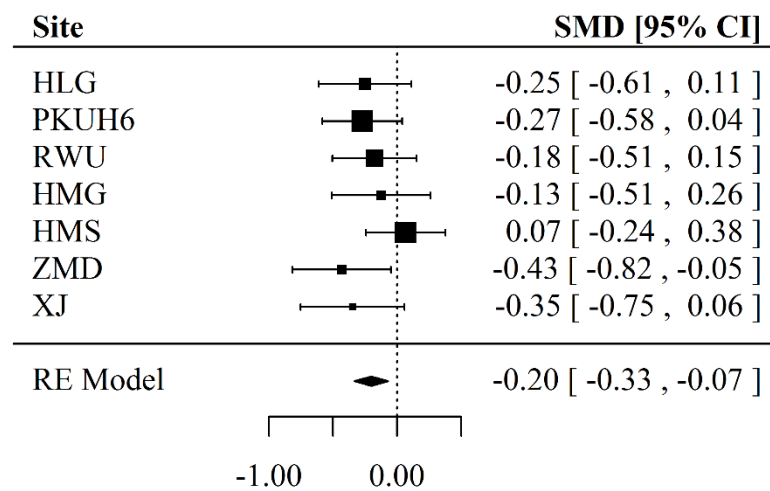
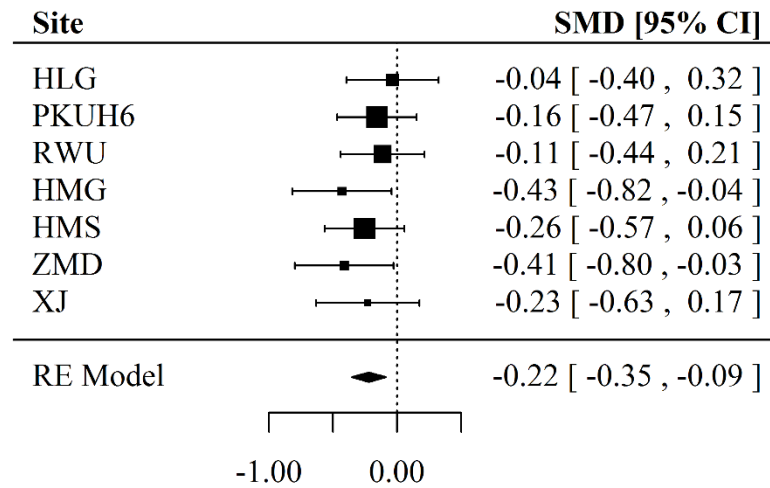


Figure 3.

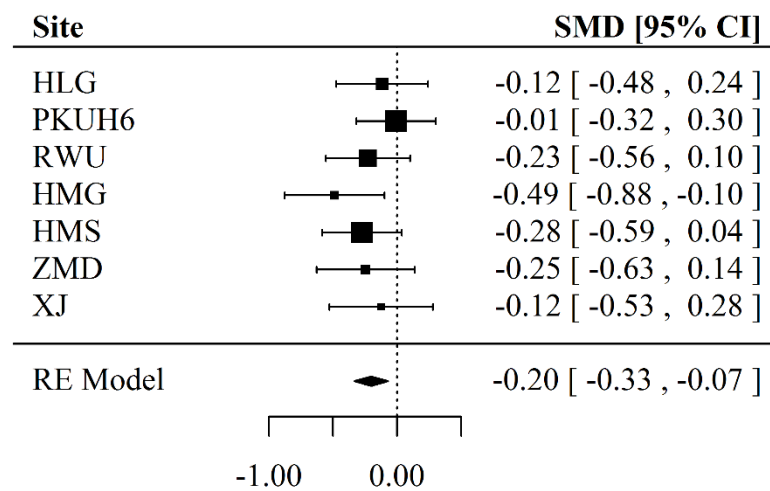
Forest plot for studies from all the sites, with standard mean difference (SMD) of FC3 as outcome.



Test for Heterogeneity: $Q(df = 6) = 3.72, p = 0.71, I^2 = 0.0\%$

Figure 4.

Forest plot for studies of FC4 from all the sites, with standard mean difference (SMD) as outcome.



Test for Heterogeneity: $Q(df = 6) = 4.23, p = 0.65, I^2 = 0.0\%$

Anatomical location	MNI coordinates		
	x	y	z
Left posterior medial frontal cortex	0	14	52
Right posterior medial frontal cortex	6	24	42
Left intraparietal sulcus/intraparietal cortex	-44	-40	42
Left anterior insular	-36	22	-2
Left inferior frontal gyrus pars opercularis	-46	10	26
Left IFG/caudal lateral prefrontal gyrus	-46	30	20
Right anterior insular	38	24	4
Right caudal lateral prefrontal cortex	34	44	26
Right inferior frontal gyrus pars opercularis	50	16	26
Right intraparietal sulcus	30	-60	50

Table# Anatomical location of the ROIs.