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Resting fMRI Measures Are Associated with Cognitive Deficits in Schizophrenia Assessed by the MATRICS Consensus Cognitive Battery

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ABSTRACT

The cognitive deficits of schizophrenia are largely resistant to current treatment, and are thus a life-long burden to patients. The MATRICS consensus cognitive battery (MCCB) provides a reliable and valid assessment of cognition across a comprehensive set of cognitive domains for schizophrenia. In resting-state fMRI, functional connectivity associated with MCCB has not yet been examined. In this paper, the interrelationships between MCCB and the abnormalities seen in two types of functional measures from resting-state fMRI—fractional amplitude of low frequency fluctuations (fALFF) and functional network connectivity (FNC) maps were investigated in data from 47 schizophrenia patients and 50 age-matched healthy controls. First, the fALFF maps were generated and decomposed by independent component analysis (ICA), and then the component showing the highest correlation with MCCB composite scores was selected. Second, the whole brain was separated into functional networks by group ICA, and the FNC maps were calculated. The FNC strengths with most significant correlations with MCCB were displayed and spatially overlapped with the fALFF component of interest. It demonstrated increased cognitive performance associated with higher fALFF values (intensity of regional spontaneous brain activity) in prefrontal regions, inferior parietal lobe (IPL) but lower ALFF values in thalamus, striatum, and superior temporal gyrus (STG). Interestingly, the FNC showing significant correlations with MCCB were in well agreement with the activated regions with highest z-values in fALFF component. Our results support the view that functional deficits in distributed cortico-striato-thalamic circuits and inferior parietal lobe may account for several aspects of cognitive impairment in schizophrenia.

Keywords: functional MRI, independent component analysis (ICA), functional network connectivity (FNC), MATRICS Consensus Cognitive Battery (MCCB), schizophrenia, fractional amplitude of low frequency fluctuations (fALFF), resting-state

1. INTRODUCTION

The cognitive deficits of schizophrenia are largely resistant to current treatment and tend to be a life-long burden of the illness. The MATRICS consensus cognitive battery (MCCB) "provides a reliable and valid assessment of cognition across a comprehensive set of cognitive domains for schizophrenia" [1]. The MCCB includes 10 neurophysiologic tests

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clustered in 7 cognitive domains [2]: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition. Despite its widespread use, the neural networks underlying MCCB performance in schizophrenia have been examined in only a few single-modality brain imaging studies [3-5]. Only one study has examined MCCB correlates of fused neuroimaging data (MEG and DTI) using joint independent component analysis [6]. A posterior visual processing network was related to reduced MEG amplitude, reduced FA and poorer MCCB composite scores in schizophrenia, suggesting the advantage of this fusion technique. Currently NIMH emphasizes the importance of "target engagement" in clinical trials [7]. Understanding the brain network organization related to MCCB performance may allow imaging assessments to be engaged early in clinical trials; hence accelerates the development of new therapeutic approaches to enhance cognition. However, in resting-state fMRI, both the functional connectivity and spatial alterations specifically associated with MCCB have not been examined. Therefore we aim to use two functional measures including fractional amplitude of low frequency fluctuations (fALFF) and functional network connectivity (FNC) to examine the functional correlates of MCCB with resting-state fMRI and to find the potential functional biomarkers of cognitive dysfunction in schizophrenia.

2. METHODS

Subjects

47 schizophrenia patients and 50 age-matched healthy controls were recruited as part of a multimodal schizophrenia center for biomedical research excellence (COBRE) study at the Mind Research Network (MRN) (http://cobre.mrn.org). The demographics and clinical scores of subjects are listed in Table 1. MCCB scores of a subject were evaluated in the same day of his/her imaging scans took place. Resting-state scans were a minimum of 5 minutes, 4s in duration (152 volumes). Subjects were asked to keep their eyes open during the scan and stare passively at a presented fixation cross, as this is suggested to facilitate network delineation compared to eyes-closed conditions and helps ensure that subjects are awake. The data were collected on a 3-Tesla Siemens Trio scanner with a 12-channel radio frequency coil, with single-shot full k-space echo-planar imaging (EPI) with ramp sampling correction using the inter commissural line (AC/PC) (anterior commissure/posterior commissure) as a reference. TR=2 s, TE=29 ms, flip angle = 75°, slice thickness = 3.5mm, slice gap = 1.05 mm, field of view (FOV) 240 mm, matrix size = 64×64, voxel size = 3.75×3.75×4.55 mm^3.

Table 1. Demographics and the correlations between MCCB composite value and specific domains, PANSS symptoms and other measures

Measure		**HC**	**SZ**	***P****	***R****
Number		50	47		
Age		36.7±12.6	35.3±12.6	0.60	0.04
Gender		20F / 30M	6F / 41M	0.01	0.17
Education		13.8±1.6	12.7±2.2	0.014	0.10
MCCB*	Composite	49.8±10.5	31.3±15.7	4.2E-09	1
	Speed of processing	51.9±9.0	35.3±13.7	1.5E-09	0.91
	Attention/Vigilance	48.3±9.9	36.0±15.1	1.4E-05	0.86
	Working memory	46.8±11.4	37.1±14.5	5.3E-04	0.83
	Verbal learning	47.4±8.9	38.0±8.6	8.4E-07	0.80
	Visual learning	49.3±9.3	36.6±12.6	1.5E-07	0.79
	Reasoning/Problem solving	54.2±9.9	46.1±11.7	5.1E-04	0.64
	Social cognition	50.8+11.1	40.5±13.0	8.3E-05	0.65
PANSS	Negative	N/A	15.1±5.4		-0.48
	Positive	N/A	15.4±5.9		-0.10

MCCB=MATRICS Consensus Cognitive Battery; PANSS= Positive and Negative Syndrome Scale. P denotes the significance value of two sample t-test performed between controls and schizophrenia patients for all measures, except gender (used chi-squared test). R* is the correlation value between MCCB composite and other measures.

Preprocessing

SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) was employed to perform fMRI preprocessing. Slice timing was performed with the middle slice as the reference frame. Images were realigned using INRIalign [8]. The fMRI data were then despiked to mitigate the impact of outliers and spatially normalized into the standard Montreal Neurological Institute (MNI) space [9] with slightly up-sampled to 3×3×3 mm^3.

Examination of Functional Correlates of MCCB

The flowchart of our analysis is shown in Figure 1. Two analyses to explore the functional measures correlated with MCCB were performed in parallel, and finally they were spatially matched to see if there are consistent and replicable interrelationships between MCCB and the abnormalities seen in both fractional amplitude of low frequency fluctuations (fALFF) [7, 10] and functional network connectivity (FNC) maps [11].

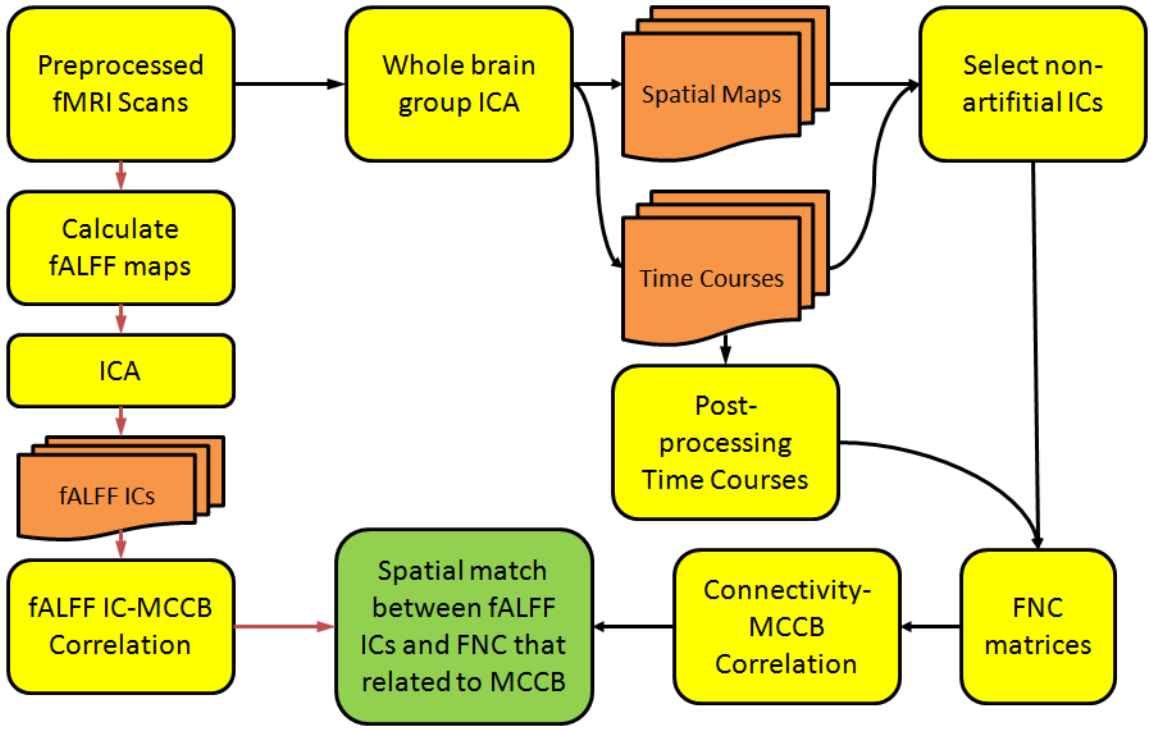

Figure 1. Flowchart to obtain the functional correlates of MCCB with fALFF and FNC. Amplitude of low frequency fluctuations (fALFF, left) and functional network connectivity (FNC, right) were calculated and correlated with MCCB respectively. Finally, the spatial maps of fALFF and FNC with high MCCB correlations were overlay for comparison and visualization.

First, the fALFF maps were computed based on the time courses of each voxel. Prior to computing ALFF, the original 4D fMRI data sets were divided by their global mean (over time and space) to normalize differences in scan intensity units. To eliminate remaining noise sources, the fMRI data underwent additional post-processing. We further regressed out 6 motion realignment parameters, white matter and CSF in de-noising, the mean framewise displacements showed no significant group difference (meanFD, mean of root of mean square frame-to-frame head motions assuming 50 mm head radius [12]; HC: 0.224±0.12mm, SZ: 0.227±0.12mm, p = 0.91). Finally, data were spatially smoothed with a Gaussian kernel with full width at half max (FWHM) of 8×8×8 mm^3. We extracted the voxel-wise fractional ALFF (fALFF) to generate a map for each subject as in [7, 10, 13, 14]. The fALFF calculation consisted of computing the fast Fourier transform on post-processed time series of each voxel, taking the square root of the power spectrum to obtain amplitude, and averaging amplitude in [0.01, 0.1] Hz [14]. The fALFF maps were then decomposed in to 8 independent sources by independent component analysis (ICA) using infomax algorithm [15]. The Pearson correlation between MCCB composite scores and loading profile of each independent component (IC) were estimated for all subjects as well as subjects in each group, and IC showing the highest correlation was selected.

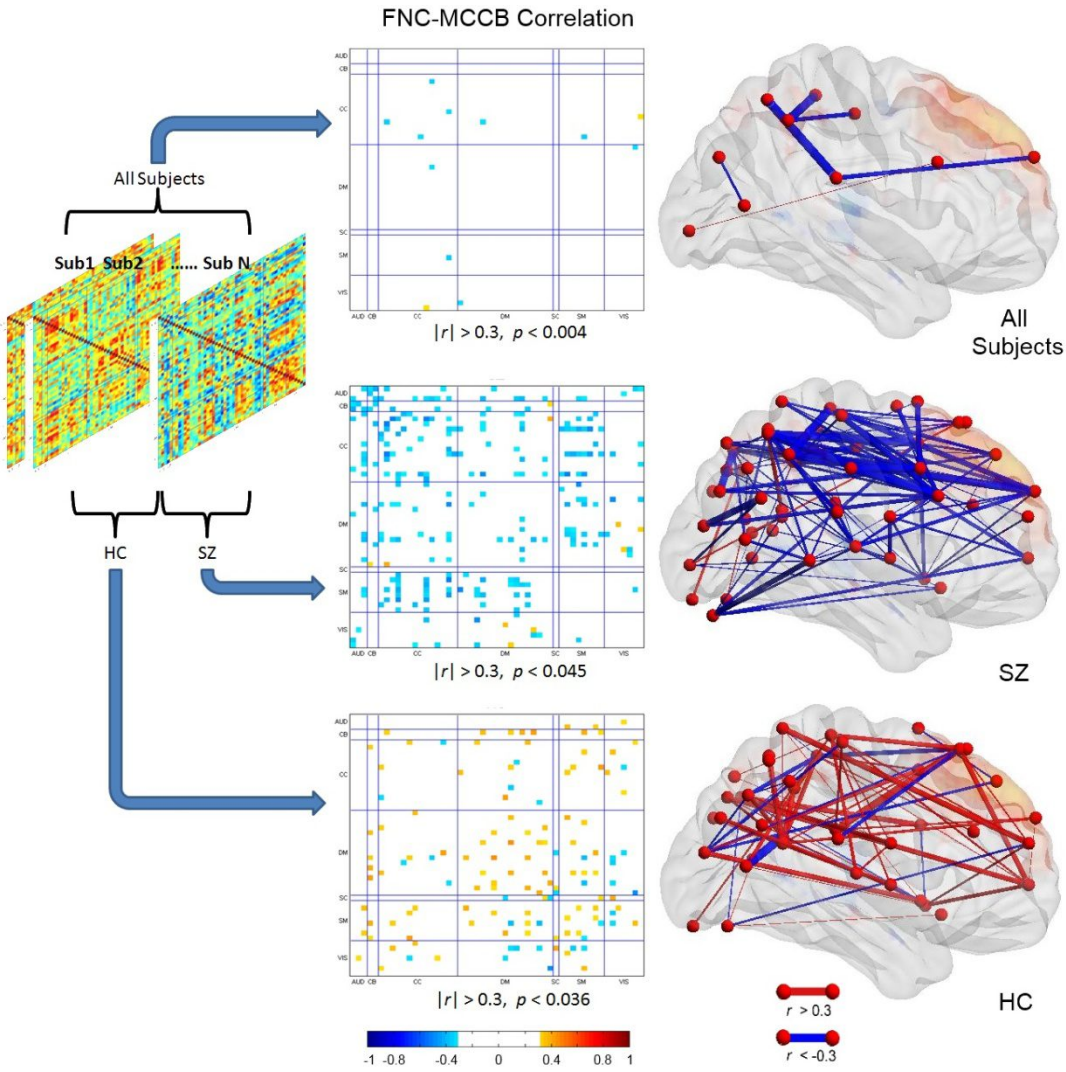

Figure 2. Correlating functional network connectivity (FNC) strengths with MCCB. The FNCs that shown in red correspond to positive correlation and those shown in blue refer to negative correlation.

Second, the whole brain fMRI images were decomposed into 100 functional networks. Group ICA was performed on preprocessed resting-state fMRI data using the GIFT software (http://mialab.mrn.org/software/gift) [16]. Individual fMRI images were decomposed via principal component analysis (PCA), with the first 120 components selected for dimension reduction. The infomax algorithm [15] was then repeated 10 times, estimating 100 group independent components via ICASSO (http://www.cis.hut.fi/projects/ica/icasso) to improve the reliability of the decomposition. Time courses and spatial ICs of individuals were then back-reconstructed [17]. Since ICs may include artifacts and noises, all ICs were manually selected for further study. The ICs selected for further FNC analysis are called intrinsic connectivity networks (ICNs), theoretically exhibited peak activations in grey matter, low spatial overlap with known vascular, ventricular, motion, and susceptibility artifacts [18]. Fifty-two non-artificial networks were characterized as ICNs, as opposed to physiological, movement related, or imaging artifacts. ICN related time courses underwent additional post-processing to remove remaining noise sources, including 1) linear, quadratic, and cubic terms for detrending, 2) multiple regression of the 6 realignment parameters and their temporal derivatives, 3) removal of detected outliers, and 4) band-pass filtering with a cutoff of [0.01, 0.1] Hz. The FNC maps were then calculated as correlation matrices across post-processed time courses of 52 ICNs. There is one 52×52 symmetric FNC matrix for each subject, with entry of element (i, j) corresponding to the strength of connectivity between ICN i and j. The connectivity-wise strengths correlations with MCCB were calculated for all subjects and subjects in each group respectively. The FNC with most significant connectivity strength-MCCB correlations were found out and shown in Figure 2. Finally, to compare the relationship

between MCCB-correlated fALFF and FNC, the ICNs connected with significant strength-MCCB correlation were spatially overlay with the z-map of fALFF IC of interest selected in the first step. The BrainNet Viewer toolbox (http://www.nitrc.org/projects/bnv/) was used for visualization [19].

3. RESULTS

In fALFF analysis, among 8 ICs derived from ICA, one IC had significant correlation with MCCB composite scores for all subjects (r = 0.25, p=0.016) and for SZ group (r = 0.36, p = 0.014). Specifically, subjects with higher MCCB scores indicated higher ALFF values in their brain areas including dorsolateral prefrontal cortex (DLPFC), superior frontal gyrus (SFG), inferior parietal lobe (IPL), and inferior frontal gyrus (IFG). At the same time, higher MCCB scores also associated lower ALFF values in left superior temporal gyrus (STG), middle temporal gyrus (MTG), thalamus, and striatum. No IC correlated with MCCB was found in HC group.

As shown in Figure 2, six FNC strengths showed significant correlation ($|r| > 0.3$) with MCCB composite scores in all subjects. Higher MCCB scores were correlated with stronger FNC between IFG and lingual, while related with weaker strengths in other five FNC, including FNCs that were connected with IPL, supplemental motor area (SMA), SFG and MTG. IPL was a hub with the most FNC strengths associated with MCCB. Detailed ICN maps are displayed in Figure 3.

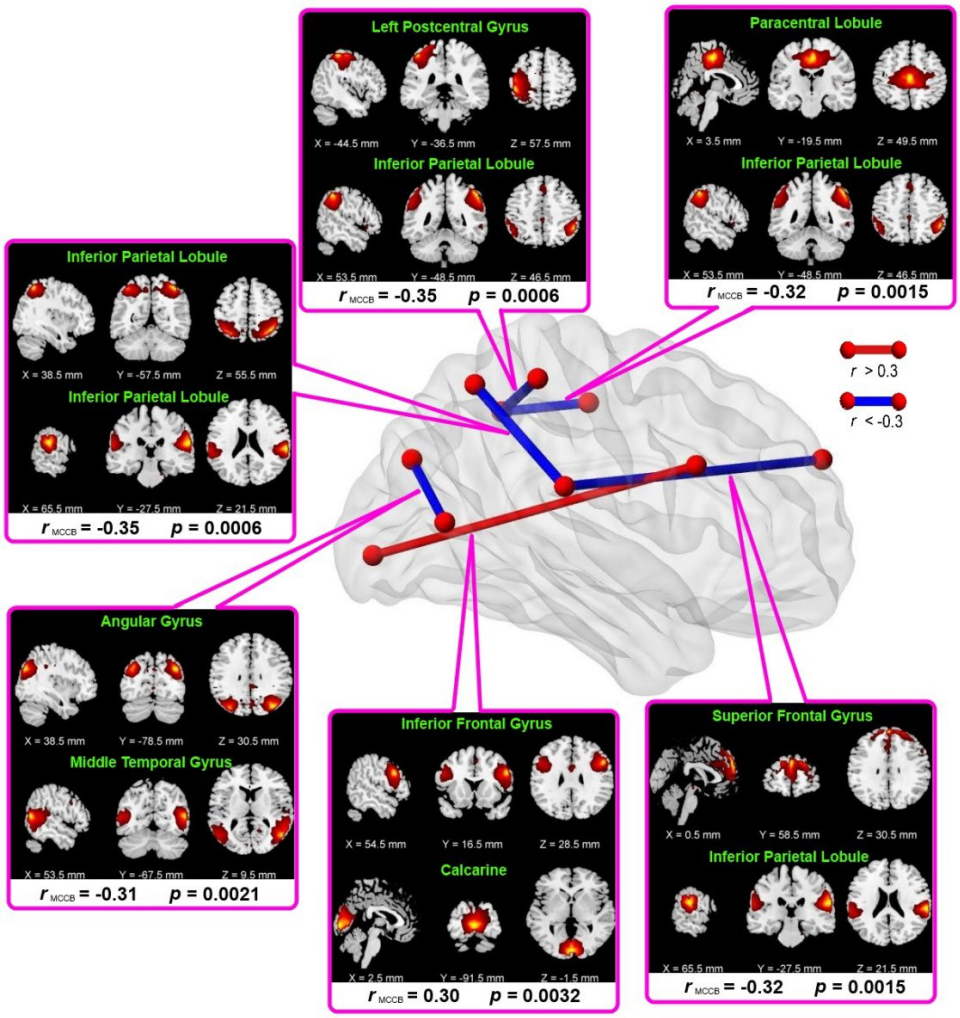

Figure 3. Six FNC strengths that showed significant correlation ($|r| > 0.3$, $p < 0.004$) with MCCB composite scores in all subjects. The FNCs that shown in red correspond to positive correlation and those shown in blue refer to negative correlation.

We also looked into the FNC strength-MCCB correlation in each group. The same threshold ($|r| > 0.3$) was used for comparison (Figure 2). There were 66 FNCs in HC and 121 FNCs in SZ with $|r| > 0.3$. The MCCB-correlations in two groups were showing in different connectivity, and with opposite trends: most FNC strengths were positively correlated with MCCB in HC, while more FNC strengths were negatively correlated with MCCB in SZ.

The overlapped MCCB-correlated FNC on fALFF 3D maps are displayed in Figure 4. Interestingly, the FNC strengths with significant correlations with MCCB were in well agreement with the activated regions with highest |z| values in fALFF IC: the high MCCB-correlated fALFF map and FNC overlaps in brain regions like prefrontal area, MTG and IPL.

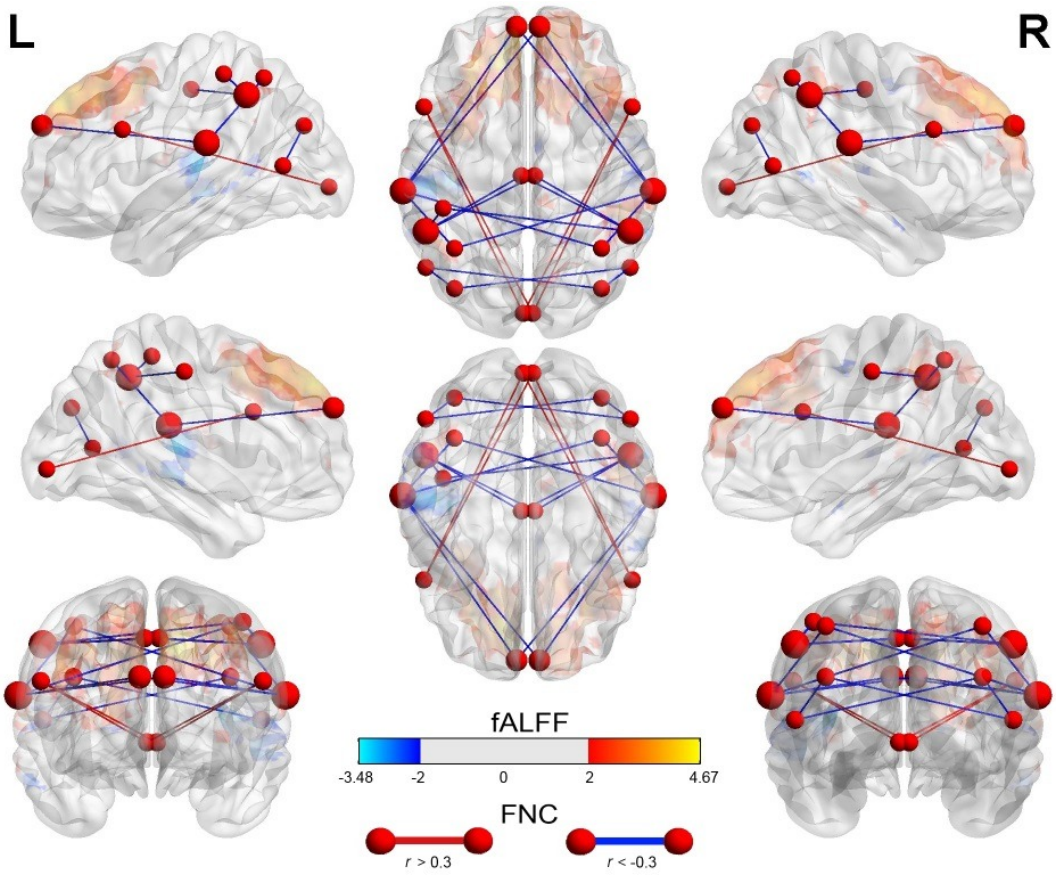

Figure 4. Overlapping MCCB-correlated FNC on 3D map of MCCB-correlated fALFF IC. The spatial map of fALFF was thresholded at |z|>2, with both positive (red regions) and the negative (blue regions) z-values. The FNCs that shown in red correspond to positive correlation and those shown in blue refer to negative correlation. Nodes represent the peak value location of ICN in each hemisphere (if an ICN is bilaterally distributed, two nodes will be shown symmetrically).

4. DISCUSSION

ALFF values correspond to intensity of regional spontaneous brain activity; while FNC describe the temporal coherence among brain regions even they are not anatomically connected. Prefrontal cortex appears in both MCCB-correlated ALFF and FNC. This region has long been demonstrated important for execution, decision making, and working memory [20-22], which are key components of evaluating the cognitive deficit [23].The brain regions including prefrontal cortex, striatum and thalamus form a cortical-striato-thalamic loop described in [24, 25]. In specific, the striatum, which is

made up of the caudate and the putamen, receives its inputs from the cortex, thalamus, hippocampus, and amygdala; then projects its output structures to thalamus; the thalamus finally projects back to the cortex, thereby completing a closed circuit [26, 27]. MCCB-correlated ALFF IC affirmed the activity in this cortical-striato-thalamic circuits affect the cognitive performance.

IPL was another hub for both MCCB-correlated ALFF and FNC. Higher fALFF values in subjects with better cognitive performance supports previous findings on IPL including angular gyrus (AG), which have been shown strong involvement in semantic processing [28], social cognition [29] or theory-of-mind [30]. The stronger FNC strengths from IPL in cognitive deficits subjects indicate the activation in IPL in those subjects is less intense, and more efforts from other brain regions may be needed to collaborate with IPL in cognitive processes.

It is worth noting that FNC strengths showed different trends with MCCB in two groups. In HC, where most high FNC-MCCB correlations were positive, indicating better cognitive performance under stronger FNC strengths. While in SZ, other FNCs showed negatively correlation with MCCB. This phenomenon may lead to FNC strengths less sensitive to MCCB when pooling all subjects together. As altered FNC structures has been reported in prior resting-state fMRI studies [31, 32], more analysis could be done to look into the impact of altered FNC topology properties on cognition impairment in future works.

5. CONCLUSIONS

This study is the first attempt to combine two approaches to investigate functional neuroimaging correlates of MCCB in schizophrenia, and both methods resulted in consistent findings. Our results support the view that functional deficits in distributed cortico-striato-thalamic circuits and inferior parietal lobe may account for several aspects of cognitive impairment in schizophrenia, placing the nature of the cognitive symptom in a new light.

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