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IN SEARCH OF NEURAL MECHANISMS OF MIRROR NEURON DYSFUNCTION IN SCHIZOPHRENIA: RESTING STATE FUNCTIONAL CONNECTIVITY APPROACH

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SUMMARY

It has been repeatedly shown that schizophrenia patients have immense alterations in goal-directed behaviour, social cognition, and social interactions, cognitive abilities that are presumably driven by the mirror neurons system (MNS). However, the neural bases of these deficits still remain unclear. Along with the task-related fMRI and EEG research tapping into the mirror neuron system, the characteristics of the resting state activity in the particular areas that encompass mirror neurons might be of interest as they obviously determine the baseline of the neuronal activity. Using resting state fMRI, we investigated resting state functional connectivity (FC) in four predefined brain structures, ROIs (inferior frontal gyrus, superior parietal lobule, premotor cortex and superior temporal gyrus), known for their mirror neurons activity, in 12 patients with first psychotic episode and 12 matched healthy individuals. As a specific hypothesis, based on the knowledge of the anatomical inputs of thalamus to all preselected ROIs, we have investigated the FC between thalamus and the ROIs. Of all ROIs included, seed-to-voxel connectivity analysis revealed significantly decreased FC only in left posterior superior temporal gyrus (STG) and the areas in visual cortex and cerebellum in patients as compared to controls. Using ROI-to-ROI analysis (thalamus and selected ROIs), we have found an increased FC of STG and bilateral thalamus whereas the FC of these areas was decreased in controls. Our results suggest that: (1) schizophrenia patients exhibit FC of STG which corresponds to the previously reported changes of superior temporal gyrus in schizophrenia and might contribute to the disturbances of specific functions, such as emotional processing or spatial awareness; (2) as the thalamus plays a pivotal role in the sensory gating, providing the filtering of the redundant stimulation, the observed hyperconnectivity between the thalami and the STGs in patients with schizophrenia might explain the sequential overload with sensory inputs that leads to the abnormal cognitive processing.

Key words: *mirror neuron system, schizophrenia, fMRI, resting state, connectivity*

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INTRODUCTION

Mirror neuron system (MNS) forms a set of specialized neurons that are involved in a number of higher motor functions and, more recently, in language processing and social cognitive processes such as empathy or social interaction (e.g. Rizzolatti & Fogassi 2014). The possible underlying mechanism that unifies these processes is that the coding of intentions occurs automatically and strictly to the activations of areas involved during the execution of the same action (Iacoboni 2009). From a bunch of task-related EEG and fMRI, several brain areas that encompass mirror neuron activity were identified. Notably, inferior frontal gyrus, superior parietal lobule, premotor cortex and superior temporal gyrus (Iacoboni & Dapretto 2006) were commonly related to as areas having mirror properties.

Patients with schizophrenia, along with positive, negative symptoms and cognitive symptoms, often experience difficulties in recognizing of other people's actions and intentions. That might result in a poor social adaptation and functioning. To date, studies demonstrated a lack of brain activation in fMRI studies (e.g. Aleman et al. 2004, Enticott et al. 2008) as well as altered electrophysiological indicators so as mu-rhythm in frontal and temporal areas during motor or social task performances (Singh et al. 2011). However, the neural mechanisms of these cognitive deficits are still unclear. One possible approach would be to study brain activity, and particularly the functional connectivity patterns of the areas that encompass mirror neurons.

Following out previous findings in elevated mu-rhythms in schizophrenia patients in the absence of the task (Garakh et al. 2015, Zaytseva et al. 2015), we assumed that these initial electrophysiological alterations might be due to the altered brain connectivity and that the baseline functional level might predefine cognitive performance. Indeed, in the absence of a task, the cerebral cortex generates rich and consistent spatio-temporal patterns of activity (Smith et al. 2012). These spontaneously emerging fluctuations in the resting state appear to map the cortex and show amplitude similar to the fluctuations that are produced when performing a task (Deco et al. 2013). It is possible that these spontaneous fluctuations represent readiness of the system to react to stimuli and keep the system close to the firing threshold (van Vreeswijk et al. 1996).

Therefore, using resting state fMRI, we aimed to investigate resting state functional connectivity in four predefined brain structures, (region of interests, ROIs), namely inferior frontal gyrus, superior parietal lobule, premotor cortex and superior temporal gyrus, known for their mirror neurons activity, in patients with first episode of schizophrenia and in a group of healthy controls. As a specific hypothesis, assuming rich anatomical inputs of thalamus to the predefined areas, we have tested the functional connectivity between the thalamus and selected ROIs.

SUBJECTS AND METHODS

Participants and study design

From the Early-Stage Schizophrenia Outcome Study (ESO study) we recruited patients with first episode of psychosis (N=12) and healthy individuals (N=12). Participants were matched by age and gender (12 males, 12 females in age range of 17 to 45, mean age 29.1). During fMRI examination, participants were instructed to stay calmly in the scanner with their eyes closed and not to think of anything in particular.

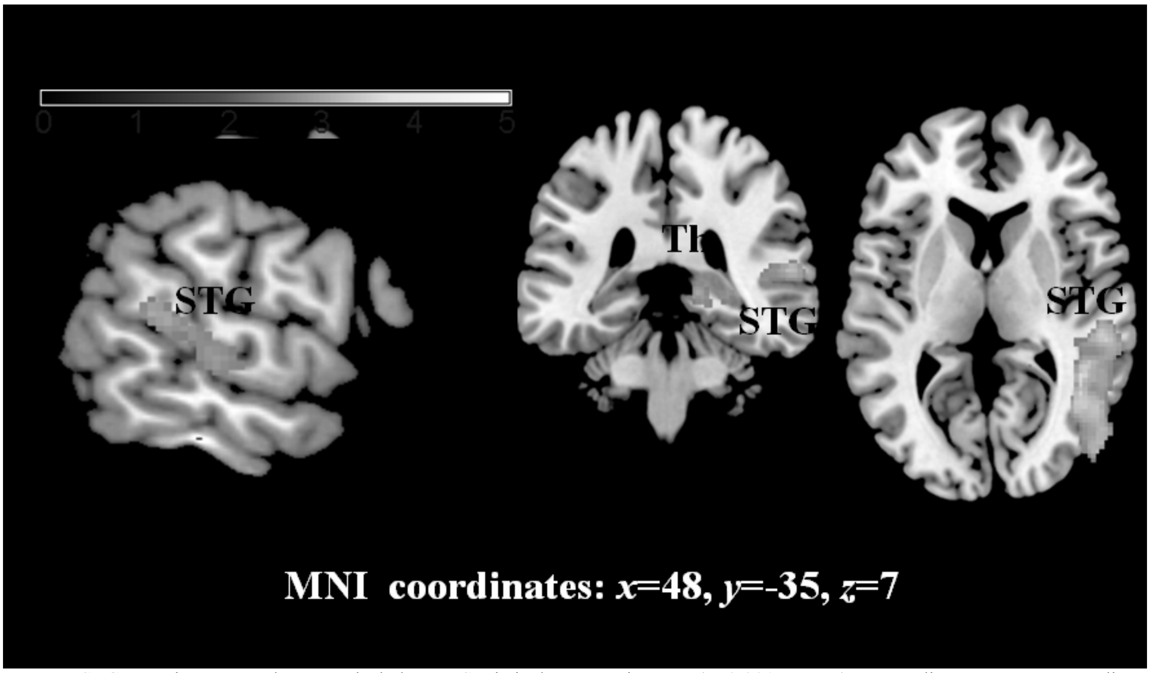
Resting state acquisition

Resting state functional scans (rsfMRI) were acquired on a 3T Siemens Tim Trio scanner during a 6-min gradient recalled EPI sequence: TR=2000 s, TE=30 ms, FOV of 1176 x1344, 300 volumes, 38 sequential ascending axial slices of 3 mm thickness and 2.99 mm gap. High-resolution structural scans were obtained using the 3D T1-weighted MPRAGE sequence (TR/TE/TI = 2300/4.63/900 ms).

Data analysis

Functional and structural data were preprocessed and analysed using tools implemented in MATLAB 01a software and SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). The preprocessing included slice-timing, motion correction, normalization to MNI space, smoothing of functional images with FWHM=8 mm. Seed-to-voxel and ROI-to-ROI connectivity analysis was done using CONN software (http://www.nitrc.org/projects/conn). Temporal filtering over the frequency band 0.008-0.09 Hz was applied.

The second-level analysis was performed using Pearson's correlation coefficients that were calculated between the mean BOLD time series of the predefined ROIs and thalamus. Correlation coefficients were converted to normally distributed z-scores by Fisher's transformation. The univariate results of seed-to-voxel analysis were presented along with the false discovery rate (FDR), multiple comparisons corrected threshold of pFDR=0.05. Significant clusters of increased or decreased functional connectivity (FC) in ROI-to-ROI in second-level analysis were determined by uncorrected threshold of cluster level P≤0.01.



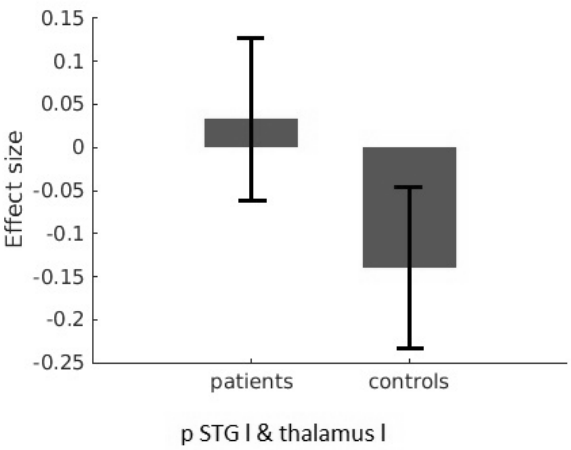
Comment: STG-superior temporal gyrus, Th-thalamus. Statistical parametric maps (p<0.001, uncorr). X coordinates are MNI coordinates.

Figure 1. Connectivity between superior temporal gyrus and thalamus

RESULTS

Firstly, the explorative seed-to-voxel analysis of the FC in preselected ROIs revealed significant FC differences only in the left posterior superior temporal gyrus (STG) in patients as compared to controls. Specifically, we have found differences in FC between the left STG (lSTG) and the left posterior temporal fusiform cortex, Z(22) =-4.52, p<0.001, p FDR-corrected =0.048, β=-0.19; left cerebelum, Z(22)=-3.77, p=0.001, p FDR-corr.=0.048, β=-0.23; vermis, Z(22)=-3.69, p=0.001, p FDR-corr.=0.048, β=-0.14; right cerebellum, Z(22)=-3.61, p=0.002, p FDR-corr.=0.048, β=-0.19; right temporooccipital fusiform cortex, Z(22)=-3.54, p=0.002, p FDR-corr.=0.048, β=-0.29; and left temporooccipital fusiform cortex, Z(22)=-3.48, p=0.002, p FDR-corr.=0.048, β=-0.27.

Secondly, using ROI-to-ROI approach, we have analysed connectivity patterns between bilateral thalami and the preselected ROIs. We have found a reverse pattern of connectivity in patients and controls between lSTG and both thalami and between right STG and left thalamus: the connectivity was increased in patients and decreased in controls. We have also found a greater variability of these results in controls than in patients (Figure 1 - 4).



Comment: STG – superior temporal gyrus

Figure 2. Connectivity between posterior left superior temporal gyrus and left thalamus

DISCUSSION

The superior temporal gyrus supposedly play a role in the emotion processing and facial stimuli response (Radua et al. 2009), although there are other functions traditionally attributed to the left and to the right STG separately. The left STG has been associated with auditory processing and language (e. g. Bigler et al. 2007), whereas the right STG has been connected with spatial awareness and exploration (Karnath et al. 2001). These functions represent a significant part of activities traditionally attributed to the MNS and impaired in schizophrenia. In previous papers (e.g. McCarley et al. 1993, Takahashi et al. 2009), it was reported that patients with schizophrenia have the reduction of grey matter volume in the superior temporal gyri. Thus, structural changes of the brain in schizophrenia, as reported, may result in the abnormal connectivity articulated in our results.

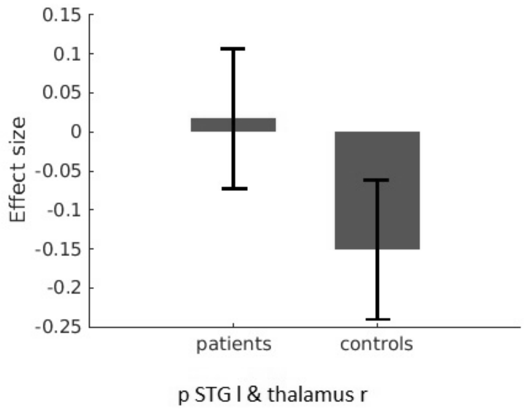


Figure 3. Connectivity between posterior left superior temporal gyrus and right thalamus

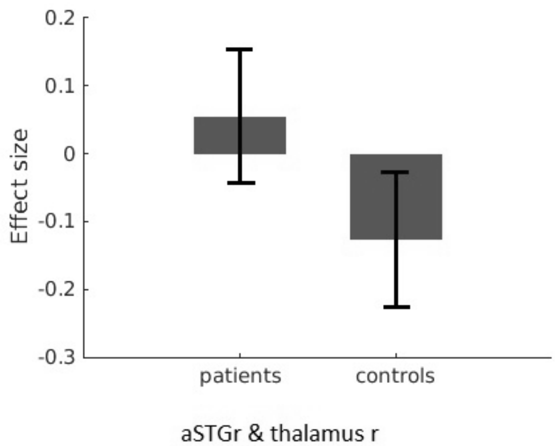


Figure 4. Connectivity between anterior left superior temporal gyrus and right thalamus

Additionally, the abnormalities in thalamus connectivity have been recently reported in patients with schizophrenia (Damaraju et al. 2014). Thus, Damaraju et al. (2014) demostrated that, in patients with schizophrenia, the thalamus was hyper-connected with the sensory networks, whereas the connectivity between sensory cortices was decreased. Our data demonstrated similar results. The connectivity between the left STG (as an auditory network) and thalamus is increased in patients as compared to controls. The reverse patterns of connectivity between the thalami and the STGs found in patients and controls, may underline diverse neural pathways that govern cognitive processing, whereas abnormal FC patterns in schizophrenia patients may result in the disturbances of specific functions, such as emotional processing or spatial awareness etc.

CONCLUSIONS

Based on our observations, it seems that the brain areas that encompass the mirror neurons and are responsible for carrying out various motor, emotional and social functions, are initially compromised in schizophrenia patients. It seems also that thalamic connections that provide sensory inputs to the MNS areas are altered as well. This may result in the abnormal sensory gating and misinterpretation of the sensory inputs leading to the alterations of the cognitive processing (McCormick & Bal 1994). Thus, the current study outlined the path for the investigation of the interrelations of cortical networks and subcortical networks. Functional connectivity approach may reinforce our understanding of the mirror neuron system in general and related cognitive processing in particular.

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Conflict of interest: None to declare.

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