Altered Thalamic Connectivity in Schizophrenia

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Introduction: Thalamus represents an information gateway between peripheral nervous system and cortex, as well as several cortical and subcortical regions. Consequently, disruption of thalamic function can generate several behavioral syndromes similar to schizophrenia [1]. In fact, several MRI studies have shown alteration in thalamic size, activation, and connectivity in this disorder [2]. The results however are rather inconsistent [3, 4]. Most of the studies considered thalamus as a single homogeneous region or used predefined anatomical landmarks for segmentation. In this study, we parcellate thalamus based on resting-state (RS) connectivity patterns in schizophrenia patients (SZ) and comparison healthy control (HC) subjects and compare the sub-regions' connectivity patterns between the two groups. We hypothesize that a more detailed study of the thalamus in schizophrenia may provide a better understanding of the mechanisms of the disorder and explain some of the discrepancies observed in previous studies.

Methods: Sixteen schizophrenia (SZ) patients and nineteen age matched healthy controls (HC) were scanned using a 3T Trio Siemens MRI scanner (Siemens Medical Solutions, Erlangen, Germany). RS-fMRI images were acquired using a gradient-echo echo planar imaging (GRE-EPI) sequence with the following imaging parameters TR/TE = 2000/29 ms, flip angle = 90°, 36 slices with slice thickness of 3.2 mm, FOV = 20 x 20 cm, matrix size = 64 x 64, and 200 volumes. Processing was performed with locally developed software and FSL and included motion correction, brain extraction, B0 field inhomogeneity correction, spatial smoothing with 5mm FWHM kernel, temporal filtering (0.01 – 0.1 Hz), and inclusion of six motion parameters, white matter, and CSF signals as regressors. To ensure that the results were not affected by head motion, framewise displacement (FD) and temporal derivative of RMS variance of the signal (DVARS) were calculated for each volume [5]. If any volume of a dataset had FD greater than 0.5 and DVARS greater than median plus one standard deviation, additional motion correction was performed by identifying and extracting motion-related components using independent component analysis (ICA) [6]. For parcellation, a similarity matrix was generated with the ij component describing the similarity between the connectivity patterns of the i^{th} and j^{th} voxels of the thalamus. Using a simulated annealing optimization algorithm [7], this similarity matrix was reordered such as voxels with similar connectivity patterns were brought close to each other to generate a block-diagonal matrix. The reordered matrix was clustered into sub-regions using a least-squared fitting algorithm [7]. Corresponding sub-regions were identified in each subject based on the similarity of their connectivity maps. Binary masks of the identified sub-regions were averaged for HC and SZ patients separately to generate group masks and show areas common to subjects in each group. Group-average connectivity maps for each group as well as group difference maps were generated using each of the identified sub-regions as seeds. To investigate the effect of parcellation, the whole thalamus' connectivity was also estimated and compared between the two groups.

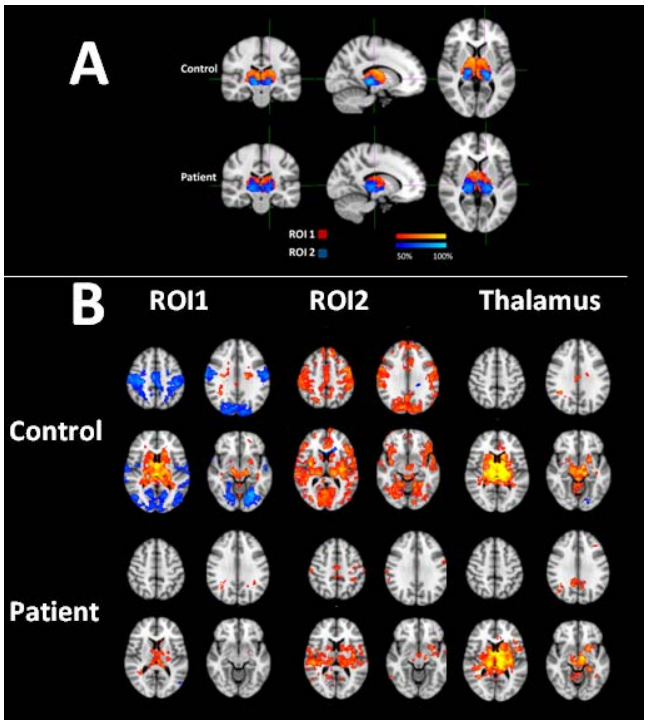

Figure 1. A) Thalamic parcellation in SZ and HC participants. B) Connectivity patterns of the ROI1, ROI2, and the whole thalamus for HC (top rows) and SZ patients (bottom rows).

Results: Thalamus was divided into dorsal (ROI1) and ventral (ROI2) ROIs in both HC and SZ patients. Figure 1A shows voxels of ROI1 and ROI2 that are common in at least 50% of each group. Connectivity maps of both sub-regions are shown in Figure 1B. In HC, ROI1 is positively connected to subcortical regions and negatively connected to motor and visual cortices. ROI2 is positively connected with the motor and visual cortices and the frontal lobe. Reduced connectivity of both ROI1 and ROI2 are observed in the SZ patients (Figure 1B, center columns). The complex thalamo-cortical connectivity observed in controls for ROI1 and ROI2 and their disruption in patients are not detectable when the whole thalamus is considered as a seed for the functional connectivity analyses (Figure 1B, rightmost columns).

Discussion: Thalamus is divided into two sub-regions that appear to have distinct connectivity patterns. The connectivity of both sub-regions appears to be disrupted in SZ patients, although the difference to HC is statistically significant only in restricted areas in the visual cortex, potentially due to the limited number of subjects participating in this study. This work highlights the importance of evaluating functionally distinct sub-regions to better understand functional connectivity in both healthy controls and patients.

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