Altered structural connectivity between patients with schizophrenia and healthy adults measured by combined direct and indirect connection strengths

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Introduction: Schizophrenia (SZ) has been widely considered as a disorder of connectivity between components of large-scale brain networks [1, 2]. Diffusion tensor imaging (DTI) studies have revealed altered white matter structural integrity in some brain regions in SZ, such as cingulum bundles (CB), uncinated fasciculus (UF), corpus callosum (CC), fornix, etc [3, 4]. In this study, we used diffusion spectrum imaging (DSI) tractography and anatomy to find physical connections between brain regions and proposed a novel definition of structural connectivity strengths between pairs of brain regions and applied the conductance concept to build edge weights for structural connectivity matrices, including direct and indirect structural connections. Our aim was to find significant differences in structural connectivity strengths between pairs of brain regions, including direct and indirect structural connections, between SZ and controls.

Methods: The connectivity matrices were constructed based on a diffusion spectrum imaging (DSI) template and a tractatlas. The DSI template was built by coregistering DSI datasets of 122 healthy adults in the Montreal Neurological Institute (MNI) space [5]. The tractatlas consisted of 74 tract bundles reconstructed in the DSI template]. 78 regions of interest (ROIs) in cortical and subcortical regions were defined to indicate two ends of a reconstructed tract bundle. Mean generalized fractional anisotropy (mGFA) of a tract bundle was determined by averaging the GFA values along the path of the entire tract bundle. The direct structural connection $SC_1(i,j)$ between ROI(i) and ROI(j) was defined as the "conductance" of a tract bundle: $SC_1(i,j)$ = mGFA. The indirect connections via 2 tract bundles $SC_2(i,j)$ was determined by treating the "conductances" of the 2 tract bundles as they were connected in series. The same principle applied to the indirect connection via 3 tract bundles $SC_3(i,j)$. The summation of the direct and indirect connections was determined by treating SC_1, SC_2 and SC_3 as 3 "conductances" in parallel. We hypothesized that it can reveal more significant differences in the summation of SC_1, SC_2 and SC_3 (SC_{1+2+3}) as compared to SC_1 only or the summation of SC_1 and SC_2 (SC_{1+2}). To demonstrate this hypothesis, DSI datasets of 54 adults with SZ ad 54 healthy adults were selected to calculate their structural connectivity matrices. We performed t-test to obtain P values which were used to judge significant differences ($p<0.05$) in structural connectivity strengths between pairs of brain regions. DSI was performed on a 3T MRI system (TIM Trio, Siemens) using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, FOV = 200 x 200 mm, image matrix size = 80 x 80, and slice thickness = 2.5 mm. A total of 102 diffusion encoding gradients with the maximum diffusion sensitivity bmax = 4000 s/mm^2 were sampled on the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units [6].

Results: The p-value matrices of SC_1, SC_{1+2}, and SC_{1+2+3} are showed in Fig. 1, Fig. 2, and Fig. 3, respectively. Black colors indicate no connection between pairs of brain regions, white colors indicate connections without significant differences ($p>0.05$), and red colors indicate connections with significant differences ($p<0.05$). In the p-value matrix of SC_1, the significant differences occur between frontal regions and temporal regions of ipsilateral hemisphere by association fibers, between cortical and subcortical regions by projection fibers except between parietal regions and subcortical regions as well as between limbic regions and subcortical regions, and between homotopic regions of bilateral hemispheres by commissural fibers. In the p-value matrix of SC_{1+2}, new significant differences occur in frontal-frontal connections, frontal-occipital connections, frontal-temporal connections in the ipsilateral hemisphere. In addition, new significant differences are also found in the inter-hemispheric connections between cortical and subcortical regions. In the p-value matrix of SC_{1+2+3}, new significant differences are found in inter-hemispheric heterotopic connections in both cortical and subcortical regions. From Figures 1-3, we can see that as 1st-degree and 2nd-degree indirect connections are added to the direct connection, the numbers of significant differences in structural connectivity strengths between pairs of brain regions between SZ and controls increase from 32 to 161.

Discussion and Conclusion: Based on the cortical and subcortical parcellation and connecting tract bundles reconstructed in the DSI template, we presented a unique method to calculate the structural connectivity strengths between pairs of ROIs, including direct and indirect structural connections, and performed t-test to obtain P values which were used to judge significant differences ($p<0.05$) in structural connectivity strengths between pairs of brain regions between SZ and controls. We found that the p-value matrix of SC_{1+2+3} can provide more significant differences information than the p-value matrix of SC_1 and the p-value matrix of SC_{1+2}. It warrants further studies to show that our proposed method of calculating structural connectivity strengths between pairs of brain regions can apply to clinical diagnosis.

References: [1] Lynall, M.E., et al., Journal of Neuroscience 2010;30(28):9477-9487. [2] Bassett, D.S., et al., Journal of Neuroscience 2010;28(37):9239-9248. [3] Kunimatsu, N., et al., Psychiatry Research 2012;201:136-143. [4] Boos, H.B., et al., European Neuropsychopharmacology 2013;23:295-304. [5] Hsu Y. et al., NeuroImage 2012;63:818-834. [6] Wedeen V., et al., Magn. Reson. Med. 2005; 54:1377-1386.

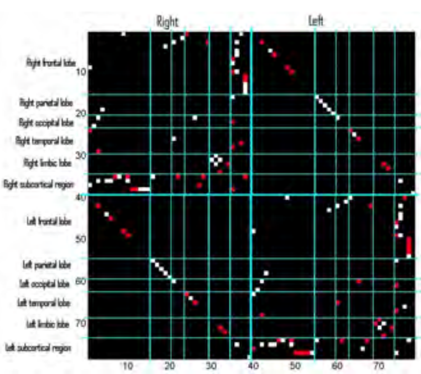

Fig. 1. The p-value matrix of SC_1 (direct connection) between SZ and controls. Black: unconnected, white: $p>0.05$, and red: $p<0.05$.

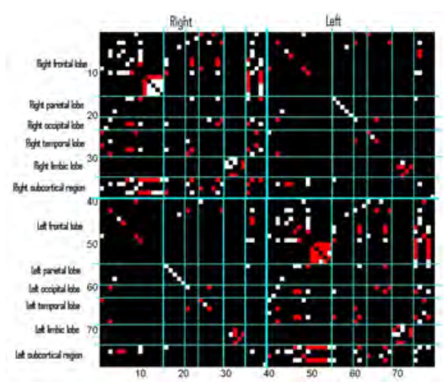

Fig. 2. The p-value matrix of SC_{1+2} (direct connection + 1st-degree indirect connection) between SZ and controls. Black: unconnected, white: $p>0.05$, and red: $p<0.05$.

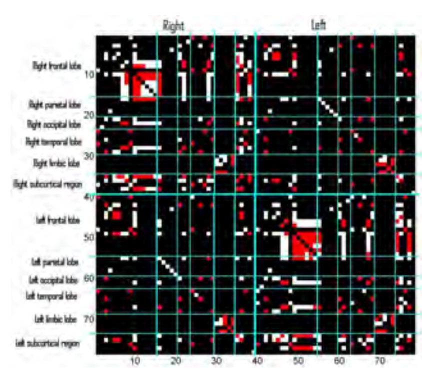

Fig. 3. The p-value matrix of SC_{1+2+3} (direct connection + 1st-degree indirect connection + 2nd-degree indirect connection) between SZ and controls. Black: unconnected, white: $p>0.05$, and red: $p<0.05$.