Abnormal morphology and connectome of neural networks in schizophrenia and unaffected sibling: a study involving PRS specific to neurotransmitter pathways

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Background: Schizophrenia is associated with cognitive impairments and alterations in large-scale brain networks, with a particular focus on the salience network (SN), frontoparietal network (FPN), and default mode network (DMN). The genetic factors influencing these networks and white matter connections are not fully understood.

Objective: This study aimed to investigate the genetic basis of structural abnormalities in patients with schizophrenia, their unaffected siblings, and healthy controls, focusing on cognitive functions, genetic risk, and brain imaging.

Methods: Participants included 188 schizophrenia patients, 47 unaffected siblings of these patients, and 136 healthy controls. Cognitive assessments, genetic testing, structural and diffusion MRI scans were conducted. Polygenic risk scores (PRSs) and sub PRS specific to neurotransmitter pathways were calculated, and brain imaging data were analyzed for cortical thickness, fiber connectivity, and topological properties.

Results: Schizophrenia patients exhibited lower cognitive performance and higher PRSs compared to unaffected siblings and healthy controls. Unaffected siblings showed intermediate cognitive impairments and PRSs, with some brain regions having similar cortical thickness as healthy controls, suggesting a compensatory process. Patients had thinner cortex and reduced connectivity in key networks compared to controls. Topological properties of DMN and limbic network (LN) showed weaker small-world characteristics in patients. Negative correlations were found between PRSs and cortical thickness/connectivity across all participants, suggesting genetic influence on brain structure and function.

Conclusion: The study provides insights into the genetic influences on brain structure in schizophrenia, highlighting the role of polygenic risk in cortical thickness, connectivity, and cognitive function. Unaffected siblings showed some preservation of brain structure despite genetic risk, indicating potential compensatory mechanisms.

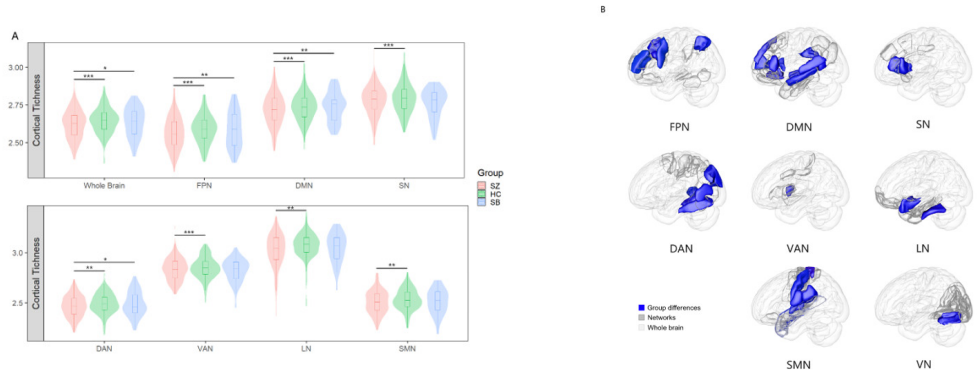

Fig. 1. Cortical thickness differences among schizophrenia patients, unaffected siblings and healthy controls. (A) Unadjusted mean thickness values of the networks in each group. (B) Brain regions of 8 networks and significant differences of cortical thickness among three groups. Note: SZ, schizophrenia patients; HC, healthy controls; SB, unaffected siblings; FPN, frontoparietal network; DMN, default mode network; SN, salience network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; VN, visual network; SMN, somatosensory-motor network.

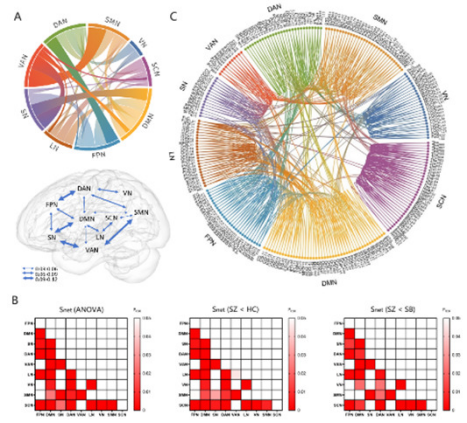

Fig.2. Differences of structural connectivity among three groups. (A) The circle in to panel represents connections between networks directly. The under panel is the sketc map of average fiber connections of networks; the line thickness represents the streng connections between networks. (B) The differences in fiber connections of networks among schizophrenia patients, unaffected siblings and healthy controls. (C) Average connections of 246 ROIs, the circle represents connections between specific brain re from each network. Note: SZ, schizophrenia patients; HC, healthy controls; SB, unaffected siblings; FPN, frontoparietal network; DMN, default mode network; SN, salience network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; VN, visual network; SMN, somatosensory-motor network; SCN, subcortical network.

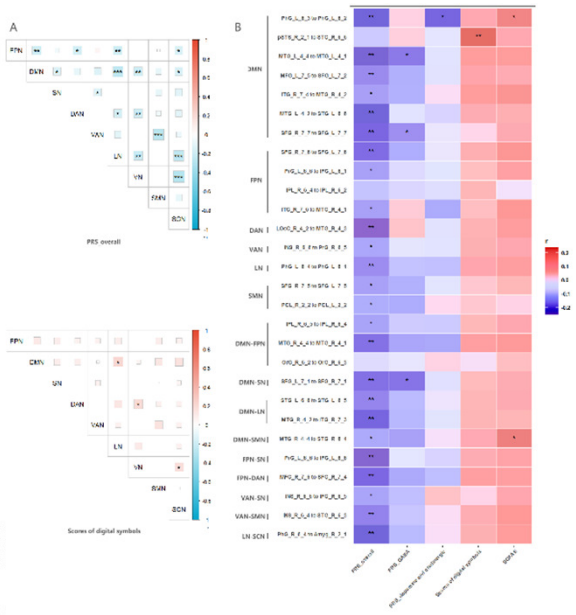

Fig. 3. The associations between PRSs, cognitive tests, SOFAS and connection features (A) (B). Note: FPN, frontoparietal network; DMN, default mode network; SN, salience network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; VN, visual network; SMN, somatosensory-motor network; SCN, subcortical network.