Disrupted small-world networks in never treated schizophrenia patients with long illness duration

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Target audience: The target audiences for this study are psychiatrists, neurologists, psychologists and radiologists.

Purpose: The hypothesis of neuroprogressive changes in schizophrenia has been a topic of increasing interest. It still remains controversial whether brain abnormalities in schizophrenia are progressive, especially in the later phase of the illness. Chronic treatment from early in the course of illness complicates efforts to address this question. The present study investigated the disruption of the topological properties of brain functional networks in a rare sample of chronic but never treated schizophrenia patients from western China to explore whether there are different age-related change patterns in these patients than healthy controls.

Methods: Twenty-two chronic schizophrenia patients with untreated illness duration over 5 years and 24 age-, gender- and years of education-matched healthy control subjects underwent a resting-state functional magnetic resonance imaging scan. The whole brain functional networks were constructed by thresholding correlation matrices of 90 cortical and sub-cortical regions, and their topological properties were analyzed using graph theory-based approaches. Nonparametric permutation tests were used for group comparisons of network and node topological metrics. The values of brain nodes that were abnormal in the patient group were extracted. We used linear modeling to test for a differential change patterns in functional metrics of these regions in patients in relation to age. Correlation was also examined with duration of untreated illness, as well as current psychopathology.

Results: Both schizophrenia and control groups showed small-world architecture in brain functional networks. However, the chronic but never treated schizophrenia patients showed altered quantitative values in the global properties, characterized by lower shortest path length, lower connection strength and lower global efficiency (Figure 1), implying a shift toward regularization in their brain networks. The schizophrenia patients exhibited decreased nodal degree and decreased nodal efficiency in right amygdala and bilateral precuneus, as well as decrease nodal clustering coefficient in left olfactory cortex and right temporal pole. The linear model demonstrated that patients showed significantly altered age-related nodal degree and efficiency changes in right amygdala relative to control subjects ($P<0.05$). Psychopathologic ratings were not found to be correlated with neither network nor nodal metrics ($p>0.05$).

Discussion: By investigating this rare sample of chronic but never treated schizophrenia patients using resting-state fMRI, the current study adds important new evidence about brain functional changes over the later illness course without the potential confounding influences of antipsychotic treatment. The schizophrenia patients showed disturbed network topological properties support the hypothesis that schizophrenia is a disorder of dysfunctional integration among large, distant brain regions.[1] The altered nodal centralities of amygdala, precuneus, olfactory and temporal pole were significantly altered (Figure 2.) consistent with the dysfunction of these areas in schizophrenia indicated by many previous studies. Furthermore, we found altered age-related node degree and efficiency in amygdala, functional deficits of amygdala at early stage of schizophrenia,[2] and progressive dysfunctional changes over the age span, indicated this region might play a crucial role in the pathological process of schizophrenia over the lifespan.

Conclusion: Our findings revealed altered global topological organization toward regularization and decreased nodal centralities in amygdala, olfactory, precuneus and putamen in later phase of schizophrenia without the potential confounding of antipsychotic treatment. Specifically, the age-related disruptions in amygdala suggested this region might act as an important component in the physiopathologic evolution of long-term schizophrenia.

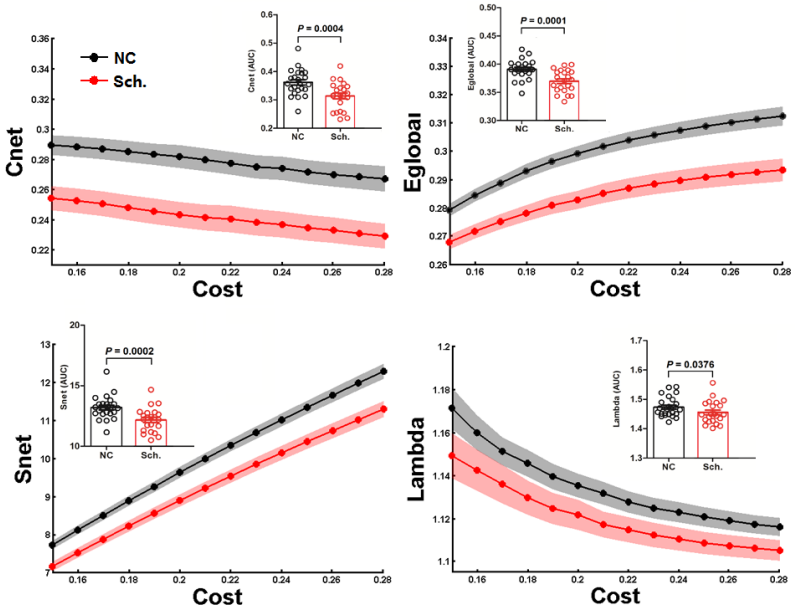

Figure 1. Cluster coefficient (Cnet), global efficiency (Eglobal), collection strength (Snet) and normalized weight characteristic shortest path length (Lambda) of the brain functional network. The shaded area indicates the standard error across subjects. The histograms show the mean value of area under curve (AUC) of subjects for network metrics (Permutation test, $P < 0.05$).

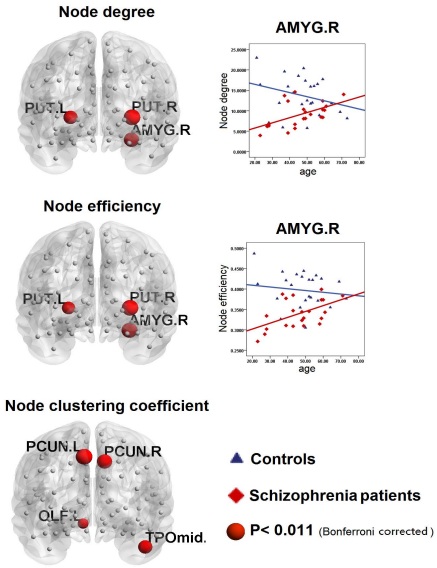

Figure 2. The left column show the nodes with decreased nodal centralities in chronic but never treated schizophrenia patients (bonferroni correction). The right column show the linear Models of the node metrics of right amygdala between patients and healthy controls ($P <0.05$).

Abbreviations: L, left; R, right; PUT, putamen; AMYG, amygdala; PCUN, precuneus; OLF, olfactory cortex; TPOmid, Temporal pole: middle temporal gyrus.

Reference: 1.Friston KJ. Disconnection and cognitive dysmetria in schizophrenia. Am J Psychiatry 2005; 162: 429 – 32

2. André Alemana, et al. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog Neurobiol. 2005 Dec; 77 (5):283-98.