# MR connectomics identifies a distributed subnetwork lesioned in schizophrenia

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## Purpose

Schizophrenia is a complex psychiatric disorder involving impaired brain connectivity[1,2]. The connectome framework[3] allows describing various aspects of the brain topology in terms of network measures, and is therefore well suited for the investigation of schizophrenia. Studies based on diffusion magnetic resonance imaging pointed out a deficiency of brain network integration, an alteration of the rich-club subnetwork[4], and a weakening of hub regions. The purpose of the present study is to build on findings related to the alteration of global brain network properties, in order to identify the brain regions that mainly contribute to such deficit. Adopting a data-driven approach, we identified a distributed subnetwork affected in schizophrenia, and quantitatively characterized the related brain network topology reorganization.

## Methods

16 schizophrenia patients (SCHZ, 10M/6F, 42yo+/-10) and 15 healthy matched controls (CTRL, 8M/7F, 41yo+/-9) underwent a magnetic resonance imaging session composed by MPRAGE and DSIq4 sequences. Subject-wise connectivity matrices were generated combining segmentation of brain tissues, parcellation of grey matter volume into 82 regions, and streamline tractography[3]. Each edge was weighted by its connection density[3], normalized by the connections densities sum over all the edges of the brain graph, therefore representing a percentage of the total connectivity amount. Global integration and segregation network properties were quantified through global efficiency and transitivity[5]. Local properties were evaluated through nodal closeness centrality and local efficiency[5], and allowed individuating a brain subnetwork altered in schizophrenia. The role of the affected subnetwork with respect to the global network topology was investigated by comparing targeted and random attacks[6]. The reorganization of the brain network communication was investigated through edge betweenness centrality and shortest paths layout. Non-parametric Mann–Whitney U test (MWU, $\alpha$=0.05) was adopted for group comparison, and multiple comparison correction was applied when necessary (FDR=0.05).

## Results

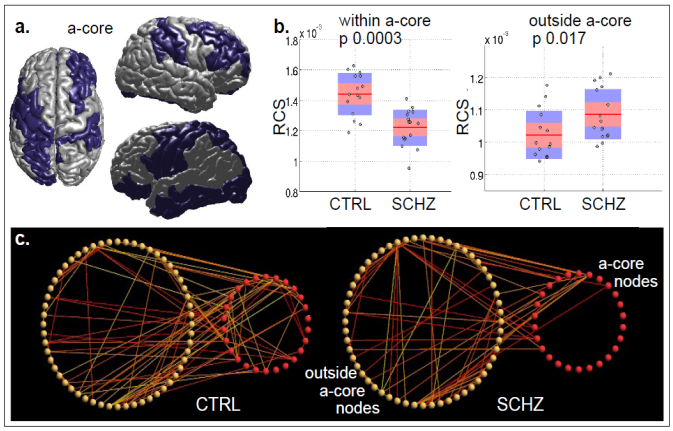
Global network efficiency was significantly decreased in schizophrenia patients with respect to controls ($p<0.009$), indicating a less efficient topological organization of the brain structural network in schizophrenia. Transitivity was as well decreased in schizophrenia subjects ($p<0.005$), suggesting a loss of segregation in the brain network organization. In order to identify the brain regions that mostly contribute to the decline of the global network properties, the single nodes were tested for decreased closeness centrality and local efficiency (one-side MWU, FDR correction). The affected nodes form a distributed subnetwork ('a-core') comprising prefrontal, middle frontal and inferior frontal cortices, parietal and left temporal areas, the basal ganglia, and the left thalamus, counting 26 nodes (a). The efficiency and the transitivity computed within the a-core were both decreased in patients compared to controls ($p<0.02$, $p<0.001$), confirming the contribution of the identified subnetwork to the global topological alterations occurring in schizophrenia. The role of the a-core with respect to the global brain network organization was investigated with a targeted attack to the a-core itself, and computing the efficiency of the surviving network ($E_s$). The topological behavior after the lesioning of the affected core was quantified through the z-score of Es computed with respect to a reference distribution. The reference distribution was estimated by repeating 1000 random attack to 26 random nodes and computing each time the efficiency of surviving network. The z-score quantifies the impact of the a-core on the global network communication: small z-scores indicate that the removal of the considered subnetwork impacts the global network topology more than by chance. The z-score for both controls and patients was significantly lower than zero ($p<0.0002$). Moreover the z-score was lower for controls compared to patients, indicating that the removal of the a-core has a more important effect on controls than on schizophrenia subjects. The identified subnetwork plays a role in the maintenance of an efficient network communication; such role is weakened in schizophrenia pathology. In order to characterize the reorganization of the brain network topology occurring in schizophrenia, the relative connection strength (RCS) and edge betweenness centrality (EBC) averaged within and outside the a-core, and the shortest paths (SPs) layout were investigated. RCS and EBC within the affected subnetwork were both decreased in patients compared to controls ($p<0.0002$, trend $p<0.1$); RCS and EBC averaged over the edges external to the affected subnetwork where both increased in patients ($p<0.02$, $p<0.03$)(b). The number of SPs between nodes not belonging to the a-core, but passing through the a-core was decreased in patients ($p<0.008$); the number of SPs between nodes not belonging to the a-core, and circumnavigating the a-core was increased in patients ($p<0.008$). This effect is qualitatively summarized in figure c, which represents the average SPs layout between nodes not belonging to the a-core, for both groups. These findings suggest a decentralization of the identified subnetwork associated to compensatory effects, leading to a less efficient global network topology.

## Discussion

In line with existing literature[1,2], our results point out an alteration of global and local network properties in schizophrenia. Particularly, a distributed sub-network comprising frontal, parietal, temporal cortices and basal ganglia was identified as major responsible for such alteration. The a-core was identified following a data-driven approach, and partially overlaps known circuits such as the rich-club, that has been shown to be affected in schizophrenia as a whole[4]. The identified subnetwork plays a substantial role in the maintenance of global network properties in both controls and patients. Nevertheless, such role appears to be weakened in schizophrenia subjects. Keeping in mind that the weight of the brain graph edges represents a percentage of the subject-wise total amount of connectivity, the decreased relative connection strength in the a-core, and its complementary increase outside the a-core, suggest a decentralization of the identified subnetwork, and indicate a re-distribution of the connection weights that penalizes the a-core nodes and is possibly associated to compensatory effects. The redistribution of the brain topology in schizophrenia leads to less efficient networks, eventually associated to the cognitive impairments underlying the pathology.

## Conclusion

Keeping in mind the technical limitations of the applied methodologies and the finite size of the considered sample, the presented findings show that in schizophrenia the loss of global structural integration and segregation is due to a distributed subnetwork which is composed of a set of nodes conveying more than expected shortest paths. In schizophrenia the lesioned subnetwork induces a reorganization of network topology with deflection of the shortest paths outside the a-core.




## References

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