Topological features of structural brain networks in sub-clinical psychosis revealed by graph theoretical analysis of tractography data

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Target Audience: Researchers and clinicians interested in using graph theory to examine brain networks in clinical conditions, particularly psychosis.

Introduction: Schizophrenia has long been conceptualised as a 'disconnection syndrome' [1]. Understanding disconnectivity in schizophrenia can benefit greatly from graph theory (GT), a powerful mathematic framework that quantifies topological features of networks beyond piecemeal analysis of network components [2]. Previous studies have reported several structural network related changes in schizophrenia by applying GT to tractography data. [3,4]. Here we elucidate structural network changes that may manifest in early prodromal stages of the disease by examining network topology in a large homogenous birth cohort who have had psychotic experiences (PEs) without a clinical diagnosis of psychosis.

Method: 248 subjects were selected from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort [5], where psychotic experiences were assessed using the PLIKS interview [6] at age 17. Those whose PEs were verified by trained researchers as suspected or definite (cases), and subjects with no such experiences (controls) were invited to undergo MRI scanning (124 cases, 126 controls). At the time of scanning all subjects were 18 years old. All data were acquired on a 3T GE HDx MRI system. HARDI acquisition: cardiac-gated EPI sequence, TE=87ms, 60 gradient orientations, 6 unweighted B0s, b-value=1200 smm^{-2}, FOV=96×96mm, 60 slices, voxel-size=1.6×1.6×2.4mm. HARDI data were analysed in ExploreDTI and corrected for motion, eddy current distortions and field inhomogeneities. The Damped Lucy-Richardson algorithm [7] was used to estimate fibre orientation distributions in each voxel and streamlines estimated with deterministic tractography (3×3×3mm grid of seed points in white matter, 1mm step size, 45° threshold). Streamlines were terminated when entering grey matter to prevent erroneous trajectories in grey matter. Tract termination points were registered to the AAL atlas, creating a 116×116 connectivity matrix. The matrices were binarised at a range of thresholds (0-20 streamlines). A range of GT metrics was computed. Network-level metrics: Global and mean efficiency, density (mean degree), mean betweenness, mean strength, global and mean clustering coefficient and smallworldness. Node-level metrics: Strength, degree, betweenness centrality, local efficiency, local clustering coefficient, modularity and path length. Independent samples t-tests were computed for all GT metrics between cases and controls. Multiple comparisons were corrected for using permutation tests (500 permutations). Additional correction for statistical bias was carried out across thresholds. Only significant (following permutation tests) effects spanning more than 6 thresholds were retained.

Results: Of the network-level metrics, network density and mean efficiency were found to be significantly lower in cases compared to controls at $p_{corr}<0.05$ (fig. 1). All other network-level metrics showed no significant differences. Of the node-level metrics, efficiency, betweenness centrality, degree and clustering coefficient all showed significant regional differences (fig. 2). Controls showed higher efficiency in several regions including inferior frontal, temporopolar, cingulate and occipitoparietal cortices. Increased degree was found in occipital and cerebellar regions. Cases showed increased betweenness centrality and clustering coefficient in supplementary motor area and orbitofrontal cortex, but the opposite effect was seen in the caudate. Cases also showed higher clustering coefficients in the insula.

Discussion: Decreased network density indicates there are fewer connections in the brains of individuals with PEs, and reduced efficiency may indicate that routing information between brain regions is impaired. The results suggest that subtle, but topologically significant changes in white matter occur, which can lead to functional changes at the network-level. These conform to previous results that show no significant difference in smallworldness in schizophrenia patients. In particular, the Zalesky et al[3] study also showed density and mean efficiency were reduced in schizophrenia. Regions showing reduced node-level efficiency overlap with many regions previously implicated by Van den Heuvel et al[4]. Betweenness centrality is higher in cases in a number of regions. Betweenness centrality is a measurement of how critical a node is to the overall network structure. Reduced connectivity in other parts of the network may make these nodes more critical in subjects with psychotic experiences. The caudate shows the opposite effect, which suggests a restructuring of the network. Similar patterns of change observed for clustering coefficient also suggests that the local topology around these regions has changed. These results are less consistent with Van den Heuvel et al[4], who show the opposite effect for most regions. It is likely that these measurements will fluctuate as different network components become impaired at different stages of psychotic illness. In conclusion, GT analysis of structural brain networks can reveal significant changes in sub-clinical conditions, which may be predictive of the development of clinically significant symptoms. Future identification of subjects who transition to clinically significant psychosis will enable more refined differentiation of GT-based predictors of psychosis.

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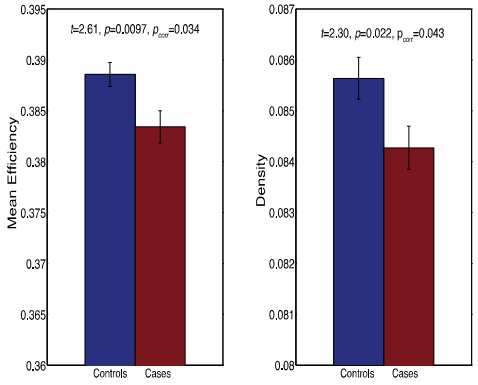

Fig. 1. Network-level GT metrics showing significant differences between case and control groups ($p_{corr}<0.05$)

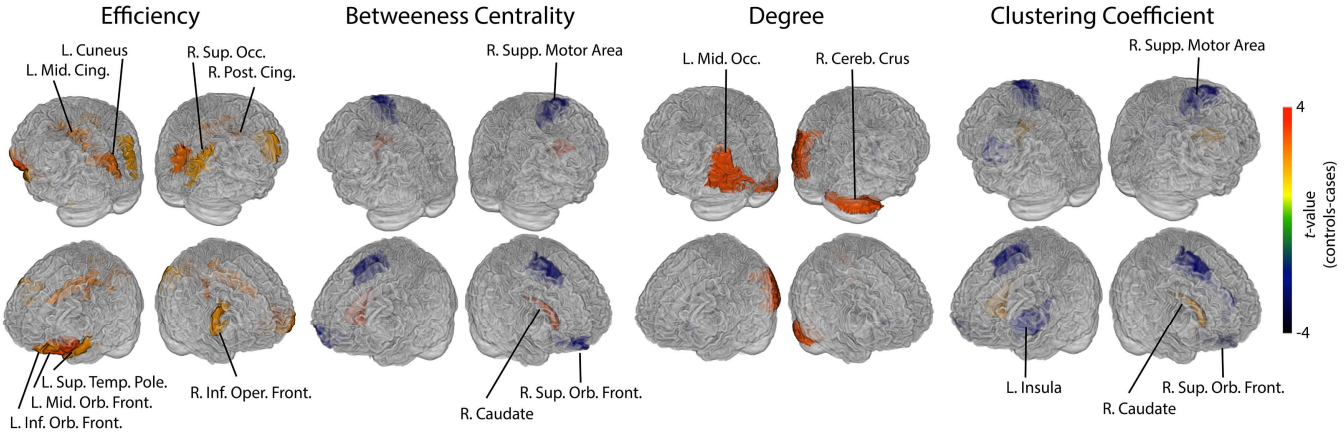

Fig 2. Node-level GT metrics showing significant differences between case and control groups ($p_{corr}<0.05$).