Development of cortical hubs in childhood and adolescence: a graph theoretical analysis in fMRI

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Introduction: The transition from late childhood to adolescence represents a critical period for brain maturation characterized by synaptic pruning and neuronal network remodeling. From a large-scale perspective, it remains unclear which brain regions are involved in network reorganization over this age range. Here, we hypothesized that topographic mapping of graph theoretical measures, namely eigenvector centrality (EC) [1], would identify brain regions that become stronger network hubs during the critical transition period. Eigenvector centrality evaluates a node's (voxel's) importance within a graph (brain) by assigning relative scores based on the principle that connections to high-scoring nodes contribute more to the score of that node than equal connections to lower-scoring nodes.

Methods: Resting state fMRI data were collected in 104 healthy subjects between the ages of 7 and 22 years (mean 14.5 years) using a 3T MRI system (Tim Trio, Siemens) and a 12-channel head coil. The protocol included a high-resolution anatomical T1 MPRAGE (1 mm iso; TR/TE/TI/FA = 2300/2.96/900/9) and a ~5 minute EPI resting state fMRI (3.5 mm iso; TR/TE/FA = 2340/30/70; 120 TRs). Following standard preprocessing (slice-timing and motion correction, spatial smoothing, bandpass filtering and whole-brain regression), Pearson correlation matrices were calculated between all voxels within a brain mask. This matrix was squared and thresholded to an Erdös-Rényi entropy of 2 [2] to ensure small-world features were consistent across all subjects [3]. Next, EC was calculated for each voxel in the brain. Each subject's EC volume was registered to the MNI152 template and correlations of each voxel with age were calculated. A non-parametric randomization algorithm, FSL randomise [4], was used to test for significant correlations and significant thresholds were determined using a threshold-free cluster enhancement algorithm.

Results: Threshold-free cluster enhancement consistently revealed brain regions that both increased and decreased significantly in EC over age. Areas that increased included the posterior cingulate cortex, ventromedial prefrontal cortex, parietal cortices and primary motor cortex, whereas decreases involved large regions of the frontal lobes, hippocampi and caudate nuclei.

Conclusions: In this large cohort of subjects, the posterior cingulate and ventromedial prefrontal cortices become stronger hubs with age while the frontal lobes and subcortical structures become weaker hubs during a critical period of development. This is consistent with differentiation in frontal lobe function during resting state with age [5]. EC-based network development analyses are a novel approach that may complement ROI-based analyses in exploring this field. Normative network development studies allow researchers to explore disease patterns that differ from this trajectory, which may give insight into areas of vulnerability for developmental delay.

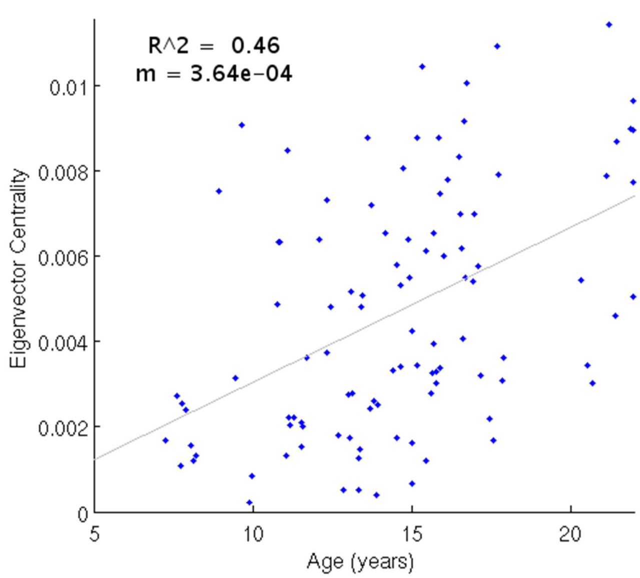

Figure 1: Correlation of eigenvector centrality in the PCC with age in each of 104 subjects.

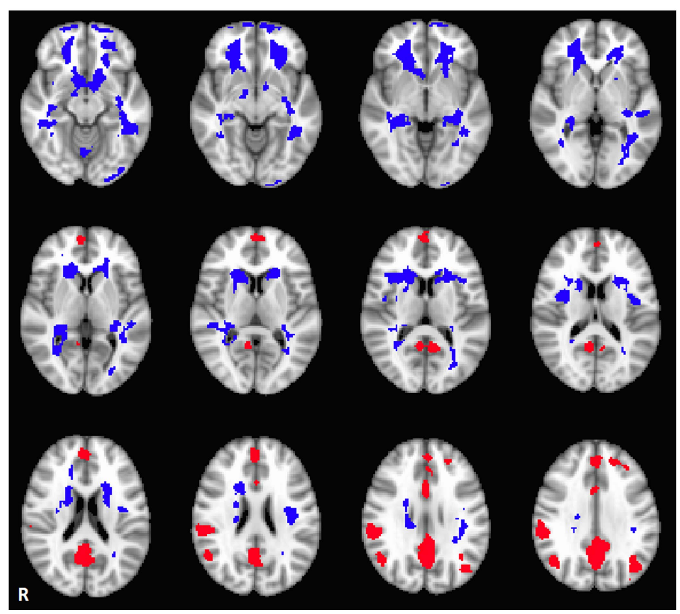

Figure 2: Montage of whole-brain eigenvector centrality correlations with age, using randomise and threshold-free cluster enhancement, corrected p<0.02. Red and blue signify positive and negative correlations, respectively.

References: [1] Rubinov and Sporns, Neuroimage, 2010. [2] Watts and Strogatz, Nature, 1998. [3] Gili, et al., J Neurosci, 2013. [4] Nicholas and Holmes, Human Brain Mapping, 2002. [5] Fair et al., PLoS computational biology, 2009.