Deterioration from Healthy to Mild Cognitive Impairment and Alzheimer's disease Mirrored in Corresponding Loss of Centrality in Directed Brain Networks

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Introduction: It is important to identify brain-based biomarkers which progressively deteriorate from healthy status to mild cognitive impairment (MCI) to Alzheimer's disease (AD). Cortical thickness [1], amyloid-β deposition [2] and graph-theoretic measures derived from resting state functional connectivity measures obtained from fMRI [3] have been identified as such potential biomarkers. Specifically in the latter case, Betweenness Centrality (BC), a local nodal characteristic which quantifies how much information may traverse the node (any given brain region), was shown to be lower in certain brain regions in both AD and MCI compared to controls [3]. However, all such reports have utilized BC calculated from undirected networks that characterize synchronization rather than information flow, which is better characterized using directed networks. Therefore, we estimated BC from directed networks derived from the application of Granger causality [4] to resting state fMRI data acquired from the following populations: Normal Control (NC), Early MCI (EMCI), Late MCI (LMCI) and AD. We used an additional metric called Middlemen Power (MP) which not only characterizes information flow through a node as in BC, but also estimates the power of the node in terms of its criticality for information flow in the entire network [5]. We tested the hypothesis that BC and MP of a few brain regions should progressively decrease from NC to EMCI to LMCI to AD.

Methods: We obtained resting state fMRI data from Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI) consisting of 98 control subjects, 87 EMCI, 87 LMCI and 61 Alzheimer's disease patients. After standard preprocessing, mean time series were extracted from 200 functionally homogeneous regions of interest (ROIs) identified via spectral clustering [6]. Latent neural signals underlying these time series were obtained using blind hemodynamic deconvolution using a Cubature Kalman filter [7] and input into a multivariate autoregressive model (MVAR) in order to obtain measures of directional influence between brain regions using correlation-purged granger causality (CPGC) [4]. The effective connectivity matrices were binarized with a threshold equal to $p<0.05$. BC and MP measures were calculated from the binarized matrices. Kintali's algorithm [8] and Sim's algorithm [5] were used to obtain BC and MP from directed networks, respectively. Six one-sided t-tests of BC and MP measures were performed (NC > EMCI, NC > LMCI, NC >AD, EMCI > LMCI, EMCI > AD, LMCI > AD), to find common nodes among all the 6 comparisons.

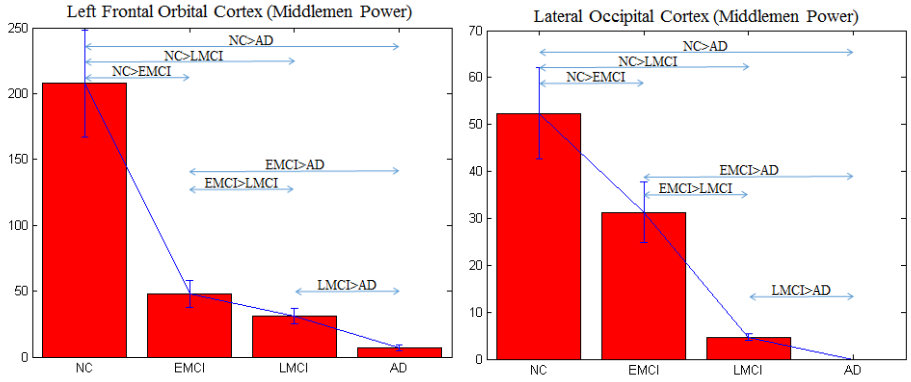

***Fig.1** Middlemen Power of Left Frontal Orbital Cortex and Lateral Occipital Cortex, which were significantly different between the groups and deteriorated from NC to EMCI to LMCI to AD*

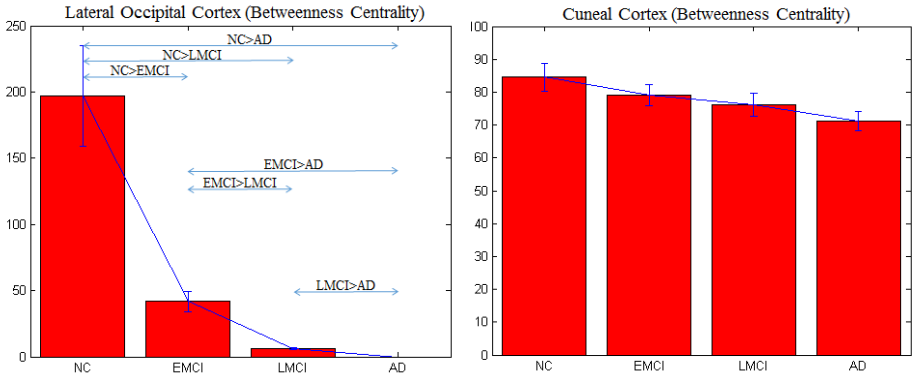

***Fig.2** Betweenness Centrality of Lateral Occipital Cortex, which was significantly different between the groups and deteriorated from NC to EMCI to LMCI to AD*

***Fig.3** Betweenness Centrality of Cuneal Cortex which was not significantly different between the groups*

Results and Discussion: MP of Left Frontal Orbital Cortex (FOC) and Lateral Occipital Cortex (LOC) progressively decreased from NC to EMCI to LMCI to AD, while BC was able to identify only the LOC and not L FOC (Figs. 1 and 2). Besides, BC estimated from undirected networks obtained from each subject using conventional functional connectivity did not identify a single node which was significant in the six t-tests mentioned above. When the threshold in all tests was lowered to $p<0.25$ (i.e. not statistically significant), Cuneal Cortex (Fig.3) was identified. This demonstrates the superiority of MP over BC obtained from both directed and undirected networks. Previous studies have shown that multimodal areas such as the LOC are more susceptible to atrophy [9], and have also demonstrated marked changes in the episodic memory network containing Left FOC [10] with neurodegeneration. Our results support these previous observations and highlight the possibility of using graph-theoretic characterization of directional brain networks obtained from resting state fMRI for tracking neurodegeneration.

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