Mapping the Alzheimer's Structural Connectome: Findings from the Alzheimer Disease Neuroimaging Initiative

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Purpose: Alzheimer's disease (AD) is a cortical, neurodegenerative dementia that accounts for 70% of all cases of dementia in the elderly. It is estimated to occur in up to 30% of individuals older than 85 years of age and currently affects nearly 5 million people in the U.S.[1] There has recently been a great deal of interest in non-invasively characterizing the structural and functional changes that occur on the continuum from normal, healthy mental function to Alzheimer's disease (AD) through the use of medical imaging. The current analysis was designed to evaluate changes in the structural connections in the brain, as assessed by connectome mapping from diffusion tensor imaging (DTI) MR scans, among normal controls (NC), subjects with mild cognitive impairment (MCI), and subjects with AD in the Alzheimer's Disease Neuroimaging Intiative 2 (ADNI2).

Methods: Subjects included in the analysis were those newly enrolled in the ADNI2 study with baseline DTI and T1-weighted SPGR scans available.[2] The ADNI2 protocol describes the acquisition protocols in depth.[3].The anatomical T1-weighted SPGR images were acquired during the same session. Each subject's anatomical images were segmented using FreeSurfer "freesurferaparc" parcellation, producing 83 regions of interest.[4] The b0 DTI scans were registered to the anatomical scans using FSL. Structural connectome maps were then constructed using the Connectome Mapper Toolkit (CMTK).[5] The anatomical parcellation was applied to the connectome map. There were eight regions, or "nodes", in each brain hemisphere that were selected for further analysis because of their known association with AD pathology and/or their known status as a structural "hub"[6,7]: precuneus, posterior cingulate, parahippocampus, entorhinal, inferior temporal, superior parietal, superior frontal, and insula. Structural connectome metrics were derived for these nodes - the weighted degree (number of fibers connected to each node), the local efficiency (the average inverse shortest path length in a node neighborhood), and the clustering coefficient (the fraction of a node's neighbors that are neighbors of each other). These metrics were calculated using the Brain Connectome Toolbox (BCT).[8] Each subject was classified as NC, MCI, or AD, based on the ADNI2 study arm criteria, which included a combination of clinical neuropsychological tests.[3] For the MCI group in this analysis, the early MCI and late MCI study arms from ADNI2 were combined. One-way ANOVA was performed with clinical diagnosis as the factor and structural network metric as the response.

Results: There were 101 ADNI2 subjects that had baseline DTI and anatomical SPGR scans available for this analysis. Characteristics of these subjects are shown in Table 1. The weighted degree of the bilateral posterior cingulate, bilateral parahippocampus, right entorhinal, and right inferior temporal nodes were of borderline statistical significance ($p < 0.10$). These regions are known to be associated with AD pathology. The bilateral insula weighted degrees were significantly associated with clinical cohort ($p < 0.05$). There were no statistically significant relationships between local efficiency or clustering coefficient as clinical diagnosis for any of the nodes analyzed.

	NC	MCI	AD
Number	37	43	21
Males	20	28	15
Females	17	15	6
Mean Age (Std)	73.7 (6.1)	71.5 (12.8)	74.9 (9.8)

Table 1. Subject characteristics.

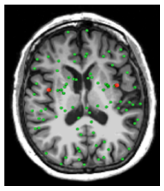

Figure 1. Nodes in connectome. Insula are in orange.

Discussion: The weighted degree of the posterior cingulate, bilateral parahippocampus, right entorhinal, and right inferior temporal nodes were of borderline significance ($p < 0.10$) when associated with clinical diagnosis. Interestingly, the bilateral insula were the only nodes which had significant associations ($p < 0.05$) between weighted degree and clinical diagnosis. The insula has been shown to be a region of high structural connectivity in the healthy brain in DTI analysis, and therefore is considered a structural "hub".[6,7] The insula is also known to exhibit pathologic changes in AD.[9]

Conclusion: Structural connectome weighted degrees demonstrate significant associations with clinical diagnosis in the ADNI2 project. Further analysis is warranted to adequately characterize these relationships, particularly using longitudinal data.

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