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Connectivity network measures predict volumetric atrophy in mild cognitive impairment

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ABSTRACT

Alzheimer's disease (AD) is characterized by cortical atrophy and disrupted anatomic connectivity, and leads to abnormal interactions between neural systems. Diffusion-weighted imaging (DWI) and graph theory can be used to evaluate major brain networks and detect signs of a breakdown in network connectivity. In a longitudinal study using both DWI and standard magnetic resonance imaging (MRI), we assessed baseline white-matter connectivity patterns in 30 subjects with mild cognitive impairment (MCI, mean age 71.8 ± 7.5 years, 18 males and 12 females) from the Alzheimer's Disease Neuroimaging Initiative. Using both standard MRI-based cortical parcellations and whole-brain tractography, we computed baseline connectivity maps from which we calculated global "small-world" architecture measures, including mean clustering coefficient and characteristic path length. We evaluated whether these baseline network measures predicted future volumetric brain atrophy in MCI subjects, who are at risk for developing AD, as determined by 3-dimensional Jacobian "expansion factor maps" between baseline and 6-month follow-up anatomic scans. This study suggests that DWI-based network measures may be a novel predictor of AD progression.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by memory loss in its early stages, typically followed by a progressive decline in other cognitive domains. People with mild cognitive impairment (MCI), a transitional stage between normal aging and AD, convert to AD at a rate of about 10%–15% per year (Bruscoli and Lovestone, 2004; Petersen et al., 2001). The Alzheimer's Disease Neuroimaging Initiative (ADNI) is one of several major efforts worldwide to identify sensitive biomarkers that may help track or predict brain tissue loss because of AD progression.

AD is marked by pervasive gray-matter atrophy, but the brain's white-matter (WM) pathways also progressively decline (Bartzokis, 2011; Braak and Braak, 1996; Braskie et al., 2011; Hua et al., 2013). Recent models of AD suggest that cognitive deficits arise from the progressive disconnection of cortical and subcortical regions, promoted by neuronal loss and WM injury (Delbeuck et al., 2003; Pievani et al., 2011). Many magnetic resonance imaging (MRI)–based image analysis methods have been used to track structural atrophy of the brain, but diffusion weighted imaging (DWI) is sensitive to microscopic WM injury not always detectable with standard anatomic MRI. DWI may be used to track the highly

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[1] Many investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but most of them did not participate in the analysis or writing of this report. A complete list of ADNI investigators may be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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anisotropic diffusion of water along axons, revealing microstructural WM fiber bundles connecting cortical and subcortical regions and allowing for characterization of the brain's WM structural network (Hagmann et al., 2008).

Graph theory network topology measures have been used increasingly to analyze brain networks and characterize network organization. "Small-world" network properties have been regarded as typical properties of many kinds of communication networks and are found in social networks, efficient biological networks, and in healthy mammalian brain networks (Achard and Bullmore, 2007; Hilgetag et al., 2000; Iturria-Medina et al., 2008; Reijneveld et al., 2007). Networks with a small-world organization can have both functional segregation and specialization of modules and a "low wiring cost" that supports easy communication across an entire network. Small-world networks are marked by low characteristic path length (CPL) and high mean clustering coefficient (MCC); so, they are both integrated and segregated. Studies using various modalities, including cortical thickness analyses, functional MRI, and electroencephalography, suggest that AD patients have abnormal small-world architecture in their large-scale structural and functional brain networks, with differences in MCC and CPL that may imply less optimal network topology (Brown et al., 2011; He et al., 2008; Sanz-Arigita et al., 2010; Stam et al., 2007; Toga and Thompson, 2013).

In this study, we assessed 30 ADNI participants showing signs of MCI. MCI subjects are the target for many clinical trials that aim to slow disease progression, before brain changes are so pervasive that they are irremediable. However, predictors of decline in MCI are sorely needed, as mildly impaired subjects do not usually exhibit drastic changes in most standard biomarkers of AD. Here, we combined DWI with longitudinally acquired standard anatomic MRI (across a 6-month interval) to measure the microstructure and connectivity of WM tracts and assess whether variations in the degree and extent of connections might predict future brain decline. We created 68 × 68 structural connectivity matrices, or graphs, that describe the strength of connections between any pair of brain regions based on baseline structural cortical parcellations and whole-brain tractography. In these graphs, "nodes" designate brain regions that are thought of as being connected by "edges" representing WM fibers. We then used graph theory to describe general properties of the anatomic networks and to characterize connectivity patterns.

Given the recent interest in "small-world" phenomena as a characteristic of biological networks, we examined whether global small-world architecture network measures, MCC and CPL, calculated from baseline connectivity maps were associated with "future" volumetric brain atrophy (dynamic tissue loss) over a 6-month follow-up period, as determined by 3-dimensional (3D) Jacobian "expansion factor maps" of T1-weighted structural scans. That is, we tested whether the intactness of the brain's anatomic network was associated with ongoing brain decline in the future, assessed using the more accepted anatomic MRI methods. In the follow-up analyses, we additionally assessed whether several baseline local nodal measures (efficiency [EFF], clustering, and betweenness [BTW] centrality) were associated with volumetric brain atrophy. We found that global and nodal network measures may offer a potentially useful biomarker for predicting longitudinal atrophy, at this critical time before the onset of AD.

2. Methods

2.1. Subject information and image acquisition

Data collection for the ADNI2 project (the second phase of ADNI) is still in progress. Here, we performed an initial analysis of 30 MCI subjects who had returned for a follow-up evaluation at 6 months (mean age at baseline 71.8 ± 7.5 years, 18 males and 12 females). We note that in ADNI2, MCI participants include the enrollment of a new early MCI cohort, with milder episodic memory impairment than the MCI group of ADNI1, now called late MCI in ADNI2 (Table 1). We additionally analyzed baseline data from 29 cognitively healthy control subjects to create a study-specific brain template (mean age at baseline 73.4 ± 5.2 years, 15 males and 14 females). Detailed inclusion and exclusion criteria are found in the ADNI2 protocol (http://adni-info.org/Scientists/Pdfs/ADNI2_Protocol_FINAL_20100917.pdf).

All subjects underwent whole-brain MRI scanning on 3-T GE Medical Systems scanners, on at least 1 of 2 occasions (baseline and 6 months). T1-weighted IR-FSPGR (inversion recovery fast spoiled gradient echo sequence) sequences (256 × 256 matrix, voxel size = 1.2 × 1.0 × 1.0 mm^3, inversion time = 400 ms, repetition time = 6.98 ms, echo time = 2.85 ms, and flip angle = 11°) and diffusion-weighted images (DWIs; 35-cm field of view, 128 × 128 acquired matrix, reconstructed to a 256 × 256 matrix, voxel size 2.7 × 2.7 × 2.7 mm^3, scan time = 9 minutes, and more imaging details may be found at http://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_GE_3T_22.0_T2.pdf) were collected. Forty-six separate images were acquired for each DWI scan: 5 T2-weighted images with no dedicated diffusion sensitization (b_0 images) and 41 DWIs (b = 1000 seconds/mm^2). The DWI protocol for ADNI was chosen after a detailed evaluation of different protocols that could be performed in a reasonable amount time; we reported results of these comparisons previously (Jahanshad et al., 2010; Zhan et al., 2012a). All T1-weighted MRIs and DWIs were checked visually for quality assurance to exclude scans with excessive motion and/or artifacts after preprocessing corrections; all scans were included.

2.2. Image preprocessing

2.2.1. Preprocessing of baseline and 6-month follow-up anatomic scans

All extracerebral tissue was removed from both baseline and 6-month T1-weighted anatomic scans using a number of software packages, primarily ROBEX, a robust automated brain extraction program trained on manually "skull-stripped" MRI data (Iglesias et al., 2011), and FreeSurfer (Fischl et al., 2004). Skull-stripped volumes were visually inspected, and the best one was selected and further manually edited. Anatomic scans subsequently underwent intensity inhomogeneity normalization using the Montreal Neurologic Institute nu_correct tool (http://www.bic.mni.mcgill.ca/software/). To align data from different subjects into the same 3D coordinate space, each anatomic image was linearly aligned to a standard brain template (the Colin27, Holmes et al., 1998) using FSL FLIRT (Jenkinson et al., 2002).

2.2.2. Baseline DWI preprocessing

For each subject, all raw DWI volumes were aligned to the average b_0 image using the FSL eddy-correct tool (http://www.fmrib.ox.ac.

Table 1
Demographics and clinical scores for the participants

	e-MCI (n = 21)	l-MCI (n = 9)	p value for group difference
			e-MCI versus l-MCI
Age (y)	71.6 ± 8.1	72.1 ± 6.6	0.87
Sex	11 M/10 F	7 M/2 F	—
Education (y)	15.8 ± 2.7	16.2 ± 3.1	0.73
MMSE	27.9 ± 1.8	27.6 ± 1.7	0.63

Key: e-MCI, early mild cognitive impairment; F, females; l-MCI, late MCI; M, males; MMSE, Mini-Mental State Examination.