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Graph theoretic analysis of structural connectivity across the spectrum of Alzheimer's disease: The importance of graph creation methods

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ABSTRACT

Graph theory is increasingly being used to study brain connectivity across the spectrum of Alzheimer's disease (AD), but prior findings have been inconsistent, likely reflecting methodological differences. We systematically investigated how methods of graph creation (i.e., type of correlation matrix and edge weighting) affect structural network properties and group differences. We estimated the structural connectivity of brain networks based on correlation maps of cortical thickness obtained from MRI. Four groups were compared: 126 cognitively normal older adults, 103 individuals with Mild Cognitive Impairment (MCI) who retained MCI status for at least 3 years (stable MCI), 108 individuals with MCI who progressed to AD-dementia within 3 years (progressive MCI), and 105 individuals with AD-dementia. Small-world measures of connectivity (characteristic path length and clustering coefficient) differed across groups, consistent with prior studies. Groups were best discriminated by the Randić index, which measures the degree to which highly connected nodes connect to other highly connected nodes. The Randić index differentiated the stable and progressive MCI groups, suggesting that it might be useful for tracking and predicting the progression of AD. Notably, however, the magnitude and direction of group differences in all three measures were dependent on the method of graph creation, indicating that it is crucial to take into account how graphs are constructed when interpreting differences across diagnostic groups and studies. The algebraic connectivity measures showed few group differences, independent of the method of graph construction, suggesting that global connectivity as it relates to node degree is not altered in early AD.

1. Introduction

Graph theory, a branch of mathematics, is increasingly being used to study the connectivity properties of structural and functional brain networks in individuals across the spectrum of Alzheimer's disease (AD) (for reviews, see Griffa et al., 2013; Tijms et al., 2013b). These investigations have been partially motivated by the finding that AD is characterized by changes in brain connectivity resulting from synaptic dysfunction and loss (Brickman et al., 2009; D'Amelio and Rossini, 2012; Scheff et al., 2011; Scheff and Price, 2006; Selkoe, 2002), as well as neuronal loss and global atrophy (Braak and Braak, 1991; Gomez-Isla et al., 1996; Kordower et al., 2001; Whitwell et al., 2012). In fact, the progressive synaptic and neural degeneration across the continuum of AD has led to the proposal that AD may be considered a 'disconnection syndrome' (for a review, see Delbeuck et al., 2003), whereby the normal functional and structural connectivity of the brain becomes increasingly disturbed. Although the precise mechanisms underlying neuronal injury in AD are unclear, it is hypothesized to result from the aggregation of β-amyloid and tau (Fein et al., 2008; Henkins et al., 2012; Takahashi et al., 2010), the two neuropathological hallmarks of AD.

Graph theory provides a set of tools that can be used to quantify the connectivity patterns of complex networks. In this framework, 'nodes' represent brain regions and 'edges' the network connections between them. Based on the number and distribution of the edges, a variety of measures can be computed to describe global and local connectivity properties (for an overview, see Rubinov and Sporns, 2010). The application of graph theory to the study of AD is appealing because AD pathology progresses throughout the brain in an orderly fashion (Braak and Braak, 1991), suggesting that connectivity properties may

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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also change in an ordered manner over the course of the disease and may have diagnostic and prognostic utility.

Prior graph theoretic studies of AD dementia and Mild Cognitive Impairment (MCI) have used a variety of methods, including structural MRI (He et al., 2008; Li et al., 2012; Tijms et al., 2013a, 2014; Yao et al., 2010) and diffusion tensor imaging (DTI) (Bai et al., 2012; Lo et al., 2010; Shu et al., 2012; Sun et al., 2014) to study anatomic connectivity, as well as resting state functional MRI (rsfMRI) (Sanz-Arigita et al., 2010; Sun et al., 2014; Supekar et al., 2008; Zhao et al., 2012), electroencephalography (EEG) (de Haan et al., 2009; Stam et al., 2007), and magneto-encephalography (MEG) (de Haan et al., 2012a; Stam et al., 2009) to study functional connectivity. Although there is agreement among these studies that AD dementia and Mild Cognitive Impairment are associated with changes in network properties, there is surprisingly little agreement about the nature of these changes. For example, inconsistent results have been reported for the two metrics that have been most frequently examined: characteristic path length, a measure of the average network distance between regions, and the clustering coefficient, a measure of local interconnectivity. Some studies have reported increases in the clustering coefficient as a function of disease severity (He et al., 2008; Yao et al., 2010; Zhao et al., 2012), others have reported a decrease (Li et al., 2012; Stam et al., 2009; Sun et al., 2014; Tijms et al., 2013a) and still others found no difference (Bai et al., 2012; Lo et al., 2010; Sanz-Arigita et al., 2010; Stam et al., 2007). Likewise, for the characteristic path length, AD-related increases (Bai et al., 2012; He et al., 2008; Lo et al., 2010; Shu et al., 2012; Yao et al., 2010; Zhao et al., 2012) and decreases have been reported (Sanz-Arigita et al., 2010; Tijms et al., 2013a, 2014).

While some of the variability in prior findings likely reflects differences in the underlying biological substrates of the networks (e.g., white matter fiber track networks, cortical thickness networks, or resting state functional networks), part of the inconsistency may also reflect methodological differences in network creation. For example, some studies used *binary edges*, whereby the strength of all connections is weighted equally (He et al., 2008; Li et al., 2012; Shu et al., 2012; Stam et al., 2007; Supekar et al., 2008; Tijms et al., 2013a; Yao et al., 2010), while others have used *weighted edges*, meaning that connections can differ in strength (Bai et al., 2012; Lo et al., 2010; Stam et al., 2009; Sun et al., 2014). Additionally, different methods have been used to construct the correlation matrix (or adjacency matrix) that is used to determine the presence of an edge, such as ordinary Pearson correlations (e.g., Li et al., 2012; Sun et al., 2014; Tijms et al., 2013a, 2014; Yao et al., 2010), partial correlations (e.g., He et al., 2008; Zhao et al., 2012), or synchronization likelihood for functional connectivity data (e.g., de Haan et al., 2012a; Sanz-Arigita et al., 2010; Stam et al., 2007). Although it has been documented that different methods of edge creation can alter the topological properties of brain graphs (e.g., Liang et al., 2012; Van Schependom et al., 2014), prior studies of AD have each used only one method of network creation and it remains unclear how different methods influence the magnitude and direction of topological differences between cognitively normal individuals, individuals with MCI, and patients with AD-dementia.

The first aim of the current study is to address this issue for one imaging modality, structural MRI, by investigating how cortical thickness (CT) networks differ across the spectrum of AD as a function of the type of correlation matrix and method of edge weighting. Positive, negative, and absolute correlations were examined separately (see Gong et al., 2012), resulting in 24 different graphs that were compared. Consistent with prior studies, characteristic path length and the clustering coefficient were examined. The second aim is to investigate three graph measures that have received little or no attention in the study of AD: (1) the Randić index, a measure of assortativity, or the tendency of similar nodes to connect to one another (Randić, 1975), (2) the Fiedler value, also known as algebraic connectivity, a graph spectral measure that contains information about the global connectivity of a network (de Haan et al., 2012b; Fiedler, 1973), and (3) the normalized Fiedler value, which is similar to the Fiedler value, but normalized for the number of edges in a graph (Chung, 1997). These measures are all indices of global connectivity (for a review, see Kincaid and Phillips, 2011), which we hypothesized would be affected in AD. Lastly, to our knowledge, prior studies have not examined the utility of graph theoretic measures to predict the progression of AD. Therefore, the third aim of this study is to examine the predictive utility graph measures for differentiating patients with stable and progressive MCI, based on their CT networks obtained at baseline.

2. Methods

2.1. Subjects

All subjects in this study were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). We analyzed data available as of May 2013. ADNI is a comprehensive, multisite longitudinal study designed to identify biomarkers to predict the progression of MCI and AD. It was launched in 2003 as a public–private partnership. The MRI data used in this study was obtained at baseline from subjects enrolled in the initial phase (ADNI-1). Study subjects gave written informed consent at enrollment for data collection, storage and use for research. Each participating institution's Institutional Review Board approved the study. The data were anonymized before being made publicly available. At baseline, subjects were medically stable, free from significant neurological and psychiatric conditions, and did not have significant cerebrovascular risk factors. For additional information about ADNI, including data collection and full inclusion and exclusion criteria, see http://www.adni-info.org.

Data from four groups of subjects were included in the current study: 127 individuals who were cognitively normal at baseline and remained cognitively normal for at least 3 years (stable normal group); 104 individuals diagnosed with MCI at baseline who retained a diagnosis of MCI for at least 3 years (stable MCI group); 106 individuals who were diagnosed with MCI at baseline and progressed to AD-dementia within 3 years; and 108 participants with a baseline diagnosis of AD-dementia. All participants had an MRI scan at their baseline visit and were administered the Clinical Dementia Rating (CDR) scale (Morris, 1993). The baseline CDR score was 0 for the cognitively normal group, 0.5 for the stable and progressive MCI groups and 0.5–1 for AD-dementia group. See Table 1 for participant characteristics at baseline. One-way analyses of variance (ANOVAs) indicated that there was no age difference across diagnostic groups ($p > 0.6$), but that education differed between groups ($F = 7.45$, $p < 0.0001$), such that patients with AD-dementia had fewer years of education than the other three groups (all $p < 0.003$). A chi-square test indicated that the distribution of males and females also differed across diagnostic groups, with significantly fewer females in the Stable MCI group than in the normal and AD-dementia groups (both $p < 0.05$). To remove any effects of age, gender, and education on the resulting CT graphs, we controlled for these variables as described below.

2.2. MRI data acquisition and cortical thickness reconstructions

Standard T1-weighted MR images were acquired sagittally with different 1.5 T scanners using a three-dimensional magnetization prepared rapid gradient-echo (MPRAGE) sequence varying in repetition time and echo time with an in-plane resolution of 1.25 × 1.25 mm and 1.2 mm slice thickness. Additional details about the MRI acquisition procedures are available at the ADNI website (http://www.adni-info.org).

Cortical reconstruction and automated thickness measures were performed using the Freesurfer software, version 5.1 (Fischl and Dale, 2000), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu). Only images that passed a quality review were included in the present analyses. Cortical thickness was