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Network and connectivity

Thickness network features for prognostic applications in dementia

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ABSTRACT

Regional analysis of cortical thickness has been studied extensively in building imaging biomarkers for early detection of Alzheimer's disease but not its interregional covariation of thickness. We present novel features based on the inter-regional covariation of cortical thickness. Initially, the cortical labels of each subject are partitioned into small patches (graph nodes) by spatial k-means clustering. A graph is then constructed by establishing a link between 2 nodes if the difference in thickness between the nodes is below a certain threshold. From this binary graph, a thickness network is computed using nodal degree, betweenness, and clustering coefficient measures. Fusing them with multiple kernel learning, it is observed that thickness network features discriminate mild cognitive impairment (MCI) converters from controls (CN) with an area under curve (AUC) of 0.83, 74% sensitivity and 76% specificity on a large subset obtained from the Alzheimer's Disease Neuroimaging Initiative data set. A comparison of predictive utility in Alzheimer's disease and/or CN classification (AUC of 0.92, 80% sensitivity [SENS] and 90% specificity [SPEC]), in discriminating CN from MCI (converters and nonconverters combined; AUC of 0.75, SENS and SPEC of 64% and 73%, respectively) and in discriminating between MCI nonconverters and MCI converters (AUC of 0.68, SENS and SPEC of 65% and 64%) is also presented. ThickNet features as defined here are novel, can be derived from a single magnetic resonance imaging scan, and demonstrate the potential for the computer-aided prognostic applications.

1. Introduction

Today, Alzheimer's disease (AD) is the most common type of dementia, accounting for 60%–80% of the cases (Alzheimer's Association, 2012), for which definitive diagnosis can only be made with the histopathologic confirmation of amyloid plaques and neurofibrillary tangles. Recent reports suggest that the Alzheimer pathology begins decades before any clinical symptoms appear (Amieva et al., 2008; Braak and Braak, 1991; Braak and Del Tredici, 2011), which highlights the importance and challenge in early detection of AD.

Structural magnetic resonance imaging (sMRI, T1-weighted) offers a noninvasive way to image and analyze the structure of the brain (high tissue-contrast) at 1 mm^3resolution and is routinely used in clinical practice. Structural alterations associated with AD can be detected before the onset of clinical symptoms (Jack et al., 2010), supporting the use of structural imaging features for the early detection of AD. A large body of research on neuroimaging techniques exists for the detection of AD and for the prediction of conversion in mild cognitive impairment (MCI), including analysis of gray matter densities (Duchesne et al., 2010; Koikkalainen et al., 2011; Misra et al., 2009), hippocampal shape (Beg et al., 2013; Coupé et al., 2012; Wang et al., 2007), amyloid deposition (La Joie et al., 2012; Tosun et al., 2011; Villain et al., 2012), functional magnetic resonance imaging (MRI) (Bullmore and Sporns, 2009; Wee et al., 2012), and also employing multimodality approaches (Walhovd et al., 2010; Westman et al., 2012). sMRI features have also been successfully applied for the differential diagnosis of AD and frontotemporal disease (Du et al., 2007; Raamana et al., 2012; Woodward et al., 2010).

The early-stage neurodegeneration observed in AD is subtle and spatially distributed over the brain, which makes cortical thickness

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features an ideal imaging-biomarker for AD. Cortical thickness has been the focus of numerous studies for the detection of probable AD (Desikan et al., 2009; Dickerson et al., 2009; Eskildsen et al., 2013; Mcevoy et al., 2011; Wolz et al., 2011). These studies show that early-stage cortical thickness by itself using only baseline MRI scans proved to be useful for the early detection of AD, but with limited utility, as was shown in Cuingnet et al. (2011). Cuingnet et al. (2011) performed an objective comparison of the predictive performance of published image processing methods, on a common data set, to predict conversion to AD in MCI patients. They observed that the performance of various method based solely on baseline cortical thickness has been limited at the best in accurately predicting conversion to AD in MCI subjects.

There has been a plethora of research in ROI-based analysis of cortical thickness (Cuingnet et al., 2011), but only few studies analyzed the covariation of thickness in different regions of the brain. We would like to capture the nature of the pairwise changes to characterize the topographic covariation in cortical thickness as associated with the progression of AD. Establishing links (akin to edges in a graph) using cortical thickness or gray matter density extracted from sMRI allows for such a study, and these approaches are only beginning to be explored. Here, we briefly summarize the different studies published so far and refer the reader to the following publications for a comprehensive review of studies on anatomic covariance (Alexander-Bloch et al., 2013a; Evans, 2013; Iturria-Medina, 2013; Wen et al., 2011). These studies can broadly be divided into 2 categories based on the type of anatomic features they use, that is, whether they use cortical morphometric features (He et al., 2008) versus gray matter density and/or volume (Mechelli et al., 2005; Tijms et al., 2012; Yao et al., 2010) to establish links and whether they utilize only the cortex (Chen et al., 2008) or the brain volume entirely (Tijms et al., 2012; Wee et al., 2012) or specific volume of interest (Mechelli et al., 2005; Seeley et al., 2009). Initial studies on structural covariance were pioneered by the Alan Evans group based on the analysis of vertex-wise correlations in thickness Lerch et al. (2006). This article was followed by (Chen et al., 2008; Gong et al., 2012; He et al., 2008, 2009a; Khundrakpam et al., 2013), which revealed insights into the aberrant network properties. For example, (He et al., 2007, 2008, 2009a, 2009b) used graph-theory analysis to study the group differences in AD relative to controls (CN) and revealed an abnormal small-world architecture, significantly reduced nodal centrality, increased local efficiency (local clustering), and decreased global efficiency (increased mean path length).

Gong et al. (2012) presented a comparison of patterns of covariance in cortical thickness and that of diffusion based fiber connections. This comparison suggested that positive correlations in cortical thickness might be mediated by a fiber pathway, and that cortical thickness correlations present exclusive information, that is not offered by fiber connections. Chen et al. (2008) demonstrated the modularity of the human cortical network (based on a network of correlations in cortical thickness) and its organization into different topologic modules overlapping closely with known functional domains.

Alexander-Bloch et al. (2013b) analyzed a longitudinal data set of healthy young people and constructed structural and maturational networks based on the rate of change in thickness over time. They studied the link between maturational networks and structural networks to demonstrate the similarity in their topologic properties (global and nodal). Khundrakpam et al. (2013) studied developmental changes in structural network properties of cortical thickness and revealed a significant reduction in local efficiency, modularity, and increased global efficiency in late childhood.

Bassett et al. (2008) analyzed group differences between schizophrenia and healthy controls to show that schizophrenic patients exhibited reduced loss of frontal hubs and emergence of nonfrontal hubs. Raj et al. (2010) analyzed the covariance networks of thickness and curvature to localize seizures in temporal lobe epilepsy and present an interesting graph-level statistical analysis. Seeley et al. (2009) studied the relationship between neurodegeneration, anatomic covariance and intrinsic connectivity networks in 5 neurodegenerative syndromes. They showed that the patterns in syndrome-specific atrophy mirror that of structural and functional covariance (using the maximal atrophic region as the seed region).

These studies presented so far assert the utility of covariance properties in studying disease-related changes. However, these studies were mostly limited to either studying the existence, or lack thereof, of small world properties, for example He et al. (2008), or any group differences in covariance properties that exist between patient and CN groups, for example Bassett et al. (2008). These studies have not, to date, constructed any features from such inter-regional covariation or performed evaluation of its diagnostic utility. We propose to utilize covariation patterns in cortical thickness as an imaging biomarker for AD. The progression of AD generally follows a stereotypical spatial pattern and hence pairwise covariation between cortical surface patches will likely complement existing features for early detection based on cortical thickness. We construct novel features based on the network properties of inter-regional links in the brain defined using cortical thickness. Furthermore, we fuse these thickness network (ThickNet) features using probabilistic multiple kernel learning approach and investigate their predictive utility in the detection of prodromal AD (MCI converters) on a large cohort from Alzheimer's Disease Neuroimaging Initiative (ADNI) data set. Further, we compare its performance in discriminating between CN and AD, CN and MCI converters (MCIc), MCIc and MCI nonconverters (MCInc) as well as between CN and MCI (MCIc + MCInc, combined).

2. Methods

2.1. Data set

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. For up-to-date information, see www.adni-info.org.

Cuingnet et al. (2011) compared the performance of various published classification methods on fixed training and testing sets resulting in a comparable set of performance metrics. To enable comparison with a large set of similar methods, we utilized the same subset of 509 participants as studied in Cuingnet et al. (2011), except for a few exclusions whose cortical parcellation did not meet our quality control metrics, see Appendix for further details. We refer the reader to Cuingnet et al. (2011) for the complete description of the participants and demographics for the study cohort. Briefly, our study consists of 481 T1-weighted MR scans acquired at 1.5 T. MRI scans from the baseline visit were used when available (and from the screening visit otherwise). This gave MR images from 159 CN subjects, 56 MCIc subjects (who had converted to AD within 18 months), 130 MCI nonconverters (MCInc) subjects, and 136 AD subjects. In this article, we use the term prodromal AD to denote MCI converters (MCIc), and the 2 terms are used interchangeably.

2.2. Thickness measurement and processing

Initial cortical reconstruction and volumetric segmentation of the whole brain were performed with the Freesurfer image analysis