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Novel ThickNet features for the discrimination of amnestic MCI subtypes

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ABSTRACT

Background: Amnestic mild cognitive impairment (aMCI) is considered to be a transitional stage between healthy aging and Alzheimer's disease (AD), and consists of two subtypes: single-domain aMCI (sd-aMCI) and multi-domain aMCI (md-aMCI). Individuals with md-aMCI are found to exhibit higher risk of conversion to AD. Accurate discrimination among aMCI subtypes (sd- or md-aMCI) and controls could assist in predicting future decline.
Methods: We apply our novel thickness network (ThickNet) features to discriminate md-aMCI from healthy controls (NC). ThickNet features are extracted from the properties of a graph constructed from inter-regional covariation of cortical thickness. We fuse these ThickNet features using multiple kernel learning to form a composite classifier. We apply the proposed ThickNet classifier to discriminate between md-aMCI and NC, sd-aMCI and NC and; and also between sd-aMCI and md-aMCI, using baseline T1 MR scans from the Sydney Memory and Ageing Study.
Results: ThickNet classifier achieved an area under curve (AUC) of 0.74, with 70% sensitivity and 69% specificity in discriminating md-aMCI from healthy controls. The same classifier resulted in AUC = 0.67 and 0.67 for sd-aMCI/NC and sd-aMCI/md-aMCI classification experiments respectively.
Conclusions: The proposed ThickNet classifier demonstrated potential for discriminating md-aMCI from controls, and in discriminating sd-aMCI from md-aMCI, using cortical features from baseline MRI scan alone. Use of the proposed novel ThickNet features demonstrates significant improvements over previous experiments using cortical thickness alone. This result may offer the possibility of early detection of Alzheimer's disease via improved discrimination of aMCI subtypes.

1. Introduction

Recent reports suggest that the amyloid pathology may begin up to 20 years before any clinical symptoms appear (Amieva et al., 2008; Braak and Braak, 1991; Braak and Del Tredici, 2011). This highlights the importance of preclinical detection, which still stands as a challenge (Cuingnet et al., 2011). Therefore, there is an urgent need for the development of reliable computer-assisted tools for predicting the conversion in mild cognitive impairment (MCI) due to AD.

The progression rates of clinically-diagnosed mild cognitive impairment (MCI) to dementia are reported to be about 12% per annum (Petersen, 2009). Amnestic subtype of MCI (aMCI) is found to have the highest conversion rate to AD as compared to other dementias (Yaffe et al., 2006). Researchers have categorized aMCI into two broad sub-types of aMCI, based on the number of domains impaired: single-domain (sd-aMCI) and multiple-domain (md-aMCI) subtypes. There is evidence to suggest that md-aMCI is the most likely subtype to progress to AD (Bäckman et al., 2004) and to dementia (Alexopoulos et al., 2006; Brodaty et al., 2013). Moreover, an association between prior subtype of MCI and subsequent progression to a particular dementia is also reported (Yaffe et al., 2006). Hence differential identification of aMCI subtypes, and their relation to specific dementia diagnoses and differential rates of conversion to dementia is worth investigating (Yaffe et al., 2006).

Structural MRI (sMRI) is a widely available noninvasive method that can capture atrophy in the brain structures in terms of subcortical volumetry/shape (Beg et al., 2013; Cuingnet et al., 2011; P. Raamana et al., 2014; Raamana et al., 2014a) as well as cortical thickness features (Cuingnet et al., 2011; Eskildsen et al., 2013; Julkunen et al., 2010; Raamana et al., 2014b). Hence it would be of prognostic value to develop imaging biomarkers, based on baseline structural MRI alone, which

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can accurately discriminate between the multiple-domain subtype of aMCI and controls.

Previous work thus far mainly focused on analyzing the group differences i.e. regional differences in gray matter loss or cortical thinning. Initial attempts to study the group differences among normal controls (NC), sd-aMCI and md-aMCI were based on voxel-based morphometry (Bell-McGinty et al., 2005; Brambati et al., 2009; Whitwell et al., 2007), with few studies analyzing cortical thickness (Fennema-Notestine et al., 2009; Seo et al., 2007). When comparing sd-aMCI or md-aMCI relative to controls, most of the studies reported differences in medial temporal and inferior temporal lobes (Brambati et al., 2009; Whitwell et al., 2007), which is expected. In the same experiments, Seo et al. (2007) and Fennema-Notestine et al. (2009) reported differences in precuneus as well, suggesting the importance of precuneus as a way to detect early stage atrophy caused by AD. When comparing sd-aMCI relative to md-aMCI, Bell-McGinty et al. (2005) reported a significant loss of volume of the left entorhinal cortex and inferior parietal lobe, whereas Seo et al. (2007) reported cortical thinning in the left precuneus. In summary, these studies suggest that moderate differences exist among the subtypes, and that the structural alterations precede the development of AD (Bell-McGinty et al., 2005). They also suggest that sd-aMCI and md-aMCI clinical subtypes could possibly represent increasing severity points along the continuum between normal aging and AD (Bäckman et al., 2004; Brambati et al., 2009).

The reports from previous studies were on the existence of group-differences among the aMCI subtypes, and where the differences exist, they improve our understanding of the early stage changes caused by AD. However, the sample sizes examined have been small (except for Fennema-Notestine et al., 2009; Whitwell et al., 2007) and unbalanced e.g. 9 sd-aMCI, 22 md-aMCI, and 61 NC in Seo et al. (2007), 9 sd-aMCI, 28 md-aMCI and 47 NC in Bell-McGinty et al. (2005) and 88 sd-aMCI, 25 md-aMCI, and 145 NC in Whitwell et al. (2007). A balanced sample i.e. equal representation for each class in the cohort, is important to ensure that the primary class of interest is not severely underrepresented (Wallace et al., 2011). In a study where the goal is to identify which patients are at increased risk of conversion to dementia, it is important that aMCI (both single and multiple domain subtypes) group is not underrepresented, as in the case of Bell-McGinty et al. (2005), Seo et al. (2007), and Whitwell et al. (2007). Furthermore, it is important to evaluate the diagnostic utility of these measures, which none of the aforementioned studies have assessed based on MRI measures (Bell-McGinty et al., 2005; Brambati et al., 2009; Fennema-Notestine et al., 2009; Seo et al., 2007; Whitwell et al., 2007).

In this study, we propose a novel ThickNet-based classifier for detection of md-aMCI. Our ThickNet fusion method has been previously tested on ADNI dataset for the detection of prodromal AD (P. Raamana et al., 2014). This method utilizes imaging biomarkers based on differential changes in cortical thickness, taking into account pair-wise differences between cortical surface patches. As there is tremendous variability of cortical thickness across the population, the signature of the disease is much more visible in cortical thickness gradients taken between different brain regions, for example anterior–posterior gradients in AD as AD is known to affect cortices such as the medial temporal lobes, the precuneus, parietal areas, entorhinal cortex preferentially and early in the course of the disease. In order to capture such inter-regional gradients (or rather co-variation in general), we formulated these network features. These features will likely complement existing features for early detection based on cortical thickness. These thickness network (ThickNet) features are combined using probabilistic multiple kernel learning approach to form a composite ThickNet classifier. This classifier significantly improves the predictive power in discriminating md-aMCI from NC, compared to the mean thickness values alone (Raamana et al., 2014b). We also show that our method improves the predictive power in the sd-aMCI vs. NC and sd- vs. md-aMCI classification experiments.

2. Materials and methods

2.1. Participants

The study sample was part of the Sydney Memory and Ageing Study (MAS) program, which comprises community-dwelling, non-demented individuals recruited randomly through electoral roll from two electorates of East Sydney, Australia. Please refer to Brodaty et al. (2013) and Sachdev et al. (2010) for complete details about this study. To be eligible, participants needed to be aged between 70 and 90 years old, sufficiently fluent in English to complete the psychometric assessment and were able to consent to participate. Participants were excluded if they had a previous diagnosis of dementia, psychotic symptoms or a diagnosis of schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy (active cancer or receiving treatment for cancer, other than prostate non-metastasized, and skin cancer), or if they had medical or psychological conditions that may have prevented them from completing assessments. Participants were excluded if they had a Mini-Mental Statement Examination (MMSE; Anderson et al. (2007), Folstein et al. (1975)) score of less than 24 adjusted for age, education and non-English speaking background at study entry, or if they received a diagnosis of dementia after comprehensive assessment. The study was approved by the Ethics Committee of the University of New South Wales. The demographics for the current study sample are listed in Table 1.

2.2. MAS subsample and cognitive assessments

Participants received a comprehensive neuropsychological assessment examining the cognitive domains of memory, language, attention/processing speed, visuo-spatial function and executive functions (see Table 2 for listing of test measures). Participants were classified as having MCI according to the latest international consensus diagnostic criteria and if all of the following criteria were met — a cognitive complaint from the participant or a knowledgeable informant, cognitive impairment on objective testing, absence of dementia, and normal function or minimal impairment in instrumental activities of daily living. Cognitive impairment was defined as a test performance of 1.5 standard deviations (SDs) or more below published normative values (demographically adjusted where possible — Table 2). Participants were considered impaired in a domain if at least one measure in the domain was impaired. In this study, only amnestic type of MCI is included. If the impairment was restricted to the memory domain, it was classified as single-domain amnestic MCI (sd-aMCI). If an additional cognitive domain was impaired, it was classified as multiple-domain amnestic MCI (md-aMCI). Participants from non-English speaking background were excluded from the MCI groups because of the questionable validity of applying standard normative data to establish cognitive impairment in non-native English speakers (Kochan et al., 2010). We additionally excluded subjects whose cortical parcellation did not meet our quality control. Within the quality controlled subset, we randomly selected a subset of controls that matched in age and size with aMCI. The final selection consisted of 38 sd-aMCI, 32 md-aMCI and 42 age-matched NC.

Table 1
Demographics of aMCI and normal subjects included in this study.

Diagnostic group	Total *N*	Age in years Mean (SD)	Gender	Education in N years Mean (SD)
NC	42	78.57 (4.13)	17 M + 25 F	11.97 (3.10)
sd-aMCI	38	79.92 (4.87)	25 M + 13 F	12.68 (3.53)
md-aMCI	32	78.63 (4.44)	17 M + 15 F	11.52 (3.84)