Integrating MRI Multivariate Markers with Cognitive Neuropsychological Scores for an Optimal Decisional Space in Predicting Alzheimer's Disease

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Summary

This study proposes a statistics-based multidimensional approach to classify Alzheimer's disease (AD) and its prodromal stages using regional measures (cortical volume, cortical thickness and surface area) obtained from MRI scans and a neuropsychological test (MMSE). Normalization effect of different approaches on these measures is also studied and validated on 314 subjects. Results indicate neuropsychological test enhances classification and when combined with selected subcortical volumes yield a high classification accuracy of 92.3% for AD classification, 72.4% for amnestic mild cognitive impairment (aMCI) and 75.1% for non-aMCI, based on 2-fold cross validation using support vector machine (SVM) classifier. Also, normalization approaches and hierarchal models do not enhance performance significantly.

Introduction

Characterized as a neurodegenerative disease that progresses with time, AD is thought to be the cause of the majority of dementia cases (Duchesne et al., 2008). Early and reliable diagnosis of AD and its prodromal stage mild cognitive impairment (MCI) through imaging and volumetric calculations is not only challenging, but remains essential in search of prospective treatments, especially when longitudinal studies become more meaningful in light of this optimal multidimensional decisional space.

MCI is the transitional stage between age-related memory decline and AD, which has two subtypes: non-amnestic and amnestic, of which aMCI is frequently seen as a prodromal stage of AD. The most noticeable problem of aMCI is memory and roughly 10% to 15% of those defined as such convert to AD (Grundman et al., 2004). Non-aMCI population generally displays impairments of cognition, such as impairments in language, visuospatial awareness, and attention. These patients convert to Alzheimer's disease less often than aMCI based on a 30 months follow up study done by Fischer et al., showing that non-aMCI has a conversion rate of 26.8% compared with 48.7% for aMCI subjects (Fischer et al., 2007).

In AD research, multiple modalities of biomarkers identifying AD and MCI have been found to be effective, including structural MRI (Westman et al., 2012, Walhovd et al., 2010, Vemuri et al., 2009), functional imaging modalities like Single-Photon Emission Computed Tomography (SPECT) (Johnson et al., 1998), Positron Emission Tomography (PET) (Walhovd et al., 2010), as well as Central Spinal Fluid (CSF) (Westman et al., 2012, and Vemuri et al., 2009). These biomarkers have been widely used to guide clinicians in delineating AD from cognitively normal controls (CN).

This study aims to deduce the statistically significant MRI measures for AD classification and explore appropriate normalization schemes to enhance the classification performance.

Materials and Methods

A total of 189 subjects with 129 cognitively normal controls (CN), 69 aMCI, 56 non-aMCI and 60 AD patients are included in this study. Table 1 provides the patient demographics. All participants are from the Wien Center for Alzheimer's Disease and Memory Disorders with the Mount Sinai Medical Center, Miami Beach, FL,

USA. All subjects have taken the Folstein Mini-Mental State Examination (Folstein et al., 1983) with a minimum score of 15 out of 30.

Table 1: Patient Demographics

Group	Number of Subjects	Age	Female/ Male	MMSE
CN	129	72.9 ± 6.4	92 / 37	28.7 ± 1.4
AD	60	79.5 ± 6.9	34 / 26	22.6 ± 3.4
Non-aMCI	56	74.1 ± 6.5	36 / 20	26.9 ± 2.3
aMCI	69	75.2 ± 6.8	37 / 32	26.5 ± 2.5

Freesurfer pipeline version 5.1.0 is widely used to generate regional measures from MRI scans (Cuingnet et al., 2011, Ewers et al., 2012, Zhou et al., 2013). The number of dimensions in the classifier is determined by an incremental error analysis, which in turn defines and ranks variables on their statistical significance to be used as input to an SVM-based classification process. Classification of MCI is also conducted to study how well the proposed method can detect early stages of AD.

Results and Discussion

3.1. AD and MCI classification

Proposed approach of multivariate classification based on selected features was performed for all groups of AD, aMCI and non-aMCI separately. Table 2 provides optimal classification accuracies found in the study using the top-ranked statistically significant regions.

Table 2: Classification Accuracy

Classification Accuracy	
aMCI vs. CN	72.4 %
non - aMCI vs. CN	75.1%
AD vs. CN	92.3 %

Figure 1 shows the top two significant regions of the sub-cortex which are deemed the most significant towards the classification of the different sub-groups together with the neurophysiological score (MMSE). This demonstrates the clustering of the subjects within a 3D decisional space comprised of the most significant variables. It is seen that the significant features used in the decisional spaces vary for different classification categories indicating shifts in regional atrophy with progression of AD. The proposed method classifies AD from CN very efficiently as both groups form more compact clusters.

3.2. Normalization effect on AD classification

To study the normalization effect on the combination of different measures for AD classification, single-measure models and hierarchical models with and without normalization are both examined to find the optimal model. Single measure models include one of the regional MRI measures (subcortical volume, cortical thickness and surface area) or MMSE. A hierarchical model combines two or more of the single-measure models to examine if the interaction augments the classification process.

Table 3: Performance of Single and Hierarchical models for AD Classification with and without Normalization

	(Accuracy ,Sensitivity, Specificity)		
Model	**RAW**	**ICV**	**MT/TSA***
MMSE	(88.3, 81.0, 91.6)	-	-
Cortical volume (CV)	(83.1 ,77.9, 85.6)	(83.5, 74.4, 87.7)	-
Cortical thickness (CT)	(77.7, 74.8, 79.0)	(79.0, 78.8, 79.2)	(90.3, 78.4, 79.2)
Surface area (SA)	(71.4, 58.7, 77.2)	(88.3,42.6, 86.1)	(88.6, 61.2, 77.9)
Hierarchical Models			
MMSE + CV	(92.3, 88.2, 94.2)	(91.7, 85.8, 94.5)	-
MMSE + CT	(91.4, 85.3, 94.2)	(91.5, 86.9, 93.6)	(90.3, 90.8, 90.1)
MMSE + SA	(88.6, 76.3, 94.3)	(88.3, 80.9, 91.7)	(88.6, 80.9, 94.2)
CT + CV*	(83.1, 77.9 ,85.6)	(83.1, 75.8, 86.5)	-
SA + CT + CV*	(83.1, 77.9, 85.6)	(83.4, 78.0, 85.9)	-
MMSE + SA + CT + SV**	(92.3, 88.2, 94.2)	(91.7, 86.0, 94.4)	-

* ICV column represents where all measures are normalized with ICV
* MT/TSA column represents where cortical thickness is normalized by mean cortical thickness and surface area is normalized by total surface area

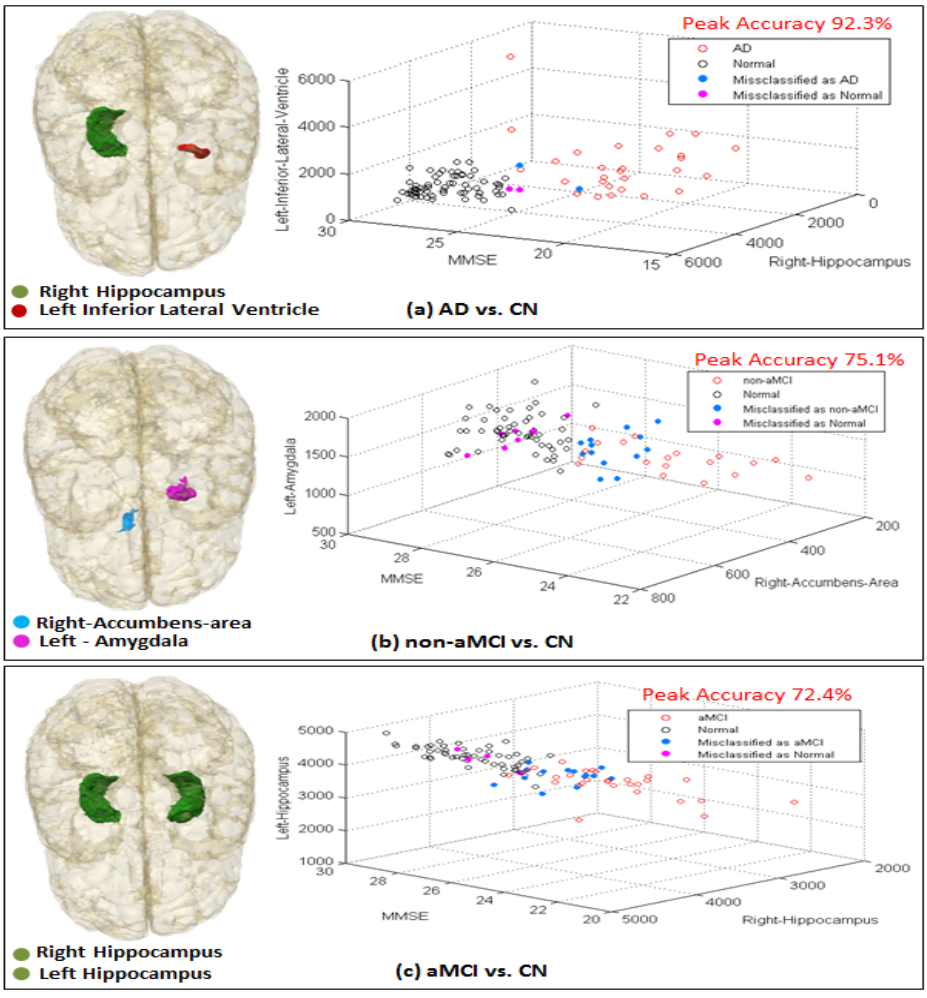

Figure 1: Top significant variables for classification of (a) AD and CN, (b) non-aMCI and CN, (c) aMCI and CN in an optimal 3D decisional feature space

The best classification (92.3 %) is obtained using hierarchal models which include sub-cortical volumes with MMSE, which is seen to have considerable effect on the classification performance with an average improvement of greater than 10%. Furthermore, the results show that cortical thickness should be normalized by either the mean thickness of all the regions or ICV, while subcortical volumes should not be normalized by ICV. However normalization doesn't enhance classification significantly if any. For some cases it even has a negative

impact. This could be explained by that current normalization approaches do not efficiently remove nuisance factors while preserving the atrophy patterns among the sub-classes.

Acknowledgment

This work is supported by the National Science Foundation under grants CNS-0959985, CNS-1042341, HRD-0833093, IIP-1230661, CNS-0821345, CNS-1126619, HRD-0833093, IIP-0829576, CNS-1057661, IIS-1052625, OISE-1157372, IIP-1237818, IIP-1215201, IIP-1026265, IIP-1058606, IIS-1213026, OISE-0730065, CCF-0938045, CNS-0747038, CNS-1018262, and CCF-0937964.

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