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A simple and clinically relevant combination of neuroimaging and functional indexes for the identification of those at highest risk of Alzheimer's disease

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ABSTRACT

The current challenge in clinical practice is to identify those with mild cognitive impairment (MCI), who are at greater risk of Alzheimer's disease (AD) conversion in the near future. The aim of this study was to assess a clinically practical new hippocampal index—hippocampal volume normalized by cerebellar volume (hippocampus to cerebellum volume ratio) used alone or in combination with scores on the Mini—Mental State Examination, as a predictor of conversion from MCI to AD. The predictive value of the HCCR was also contrasted to that of the hippocampal volume to intracranial volume ratio. The findings revealed that the performance of the combination of measures was significantly better than that of each measure used individually. The combination of Mini—Mental State Examination and hippocampal volume, normalized by the cerebellum or by intracranial volume, accurately discriminated individuals with MCI who progress to AD within 5 years from other MCI types (stable, reverters) and those with intact cognition (area under receiver operating curve of 0.88 and 0.89, respectively). Normalization by cerebellar volume was as accurate as normalization by intracranial volume with the advantage of being more practical, particularly for serial assessments.

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1. Introduction

Mild cognitive impairment (MCI) refers to modest cognitive decline along with preserved daily activities (Association, 2013). Although many people with MCI live largely normal lives, they are at higher risk of developing Alzheimer's disease (AD) than those without MCI (Forlenza et al., 2013). The available evidence suggests that less than half of patients diagnosed with MCI may progress to AD in a 5-year period while the rest remain stable or reverse to cognitively normal (CN) status (Falahati et al., 2014; Pandya et al., 2016). Generally, there is an expectation of eventual conversion from MCI to AD due to the progressive nature of the neurodegenerative processes involved, and MCI stability can depend on the duration of follow-up (Ganguli, 2013). Reversion to CN status is still an unresolved question but may relate to the relatively unspecific nature of diagnostic criteria, interaction with comorbid conditions, and/or variability in the pathological process (Park et al., 2015). Thus, the current clinical challenge is to discriminate individuals with MCI who are more likely to convert to AD.

In their revised position, the National Institute on Aging and the Alzheimer's Association (NIA-AA) considered MCI and AD as different stages of the AD continuum rather than 2 distinct clinical entities (Albert et al., 2011; Jack et al., 2018). In 2011, NIA-AA reviewed diagnostic guidelines and suggested that, owing to greater diagnostic uncertainty earlier in the AD continuum, MCI diagnosis should be supported by biological markers reflecting AD pathology (Albert et al., 2011). In 2018, the NIA-AA work group further qualified this position and recommended that biological markers should reflect neuropathological processes that define the disease instead of simply supporting the diagnosis (Jack et al., 2018). Based on this expert consensus, the work group recommended that AD biomarkers should be incorporated into MCI/AD diagnostic criteria. The NIA-AA work group identified 3 types of AD biomarkers directly related to the underlying pathological processes. The biomarkers include (1) amyloid-β deposition including cortical amyloid positron emission tomography (PET) ligand

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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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bonding (F^{18}–flutemetamol PET) and low cerebrospinal fluid (CSF) $A\beta_{42}$; (2) aggregated tau including cortical tau PET ligand bonding (flortaucipir-PET) and elevated CSF phosphorylated tau (P-tau); and (3) neurodegeneration or neural injury including PET-detected hypometabolism (fluorodeoxyglucose-PET), CSF total tau (T-tau), and cortical/volume atrophy on magnetic resonance imaging (MRI) scan (Jack et al., 2018).

Much research has been conducted to evaluate amyloid-β deposition, tau aggregation, and hypometabolism using PET scans and CSF biomarkers—separately or in combination—to classify MCI at risk of AD conversion, with some promising performance (Mitchell, 2009; Ritchie et al., 2017; Vandenberghe et al., 2013; Yuan et al., 2009). However, these methods are invasive and, especially for PET imaging, have limited availability in clinical practice. Ideally, a practical biomarker should be widely available, accurate, cost-effective, relatively simple to interpret, easy to use, and be acceptable to patients while not imposing an excessive burden. It is important that—before assessing a new biomarker—clear criteria for selection be established, and the likelihood of meeting them be considered. As a minimum, the proposed new biomarker should perform at least similar to simple, noninvasive, and currently available biomarkers.

A type of noninvasive and more widely available biomarker is provided by structural brain measurement obtained using MRI. Cerebral cortical thickness and hippocampal measures are the most predictive and practical MRI methods to date (Falahati et al., 2014; Rathore et al., 2017). Although cerebral cortical thickness has been shown to be more predictive compared to volumetric measures based on single brain regions, it requires agreement on a standard pattern of cerebral cortical thickness in AD to be adoptable in clinical practice. Hippocampal volume, which has been shown to be a moderate predictor of AD conversion with a sensitivity of 67% and specificity of 72%, has the advantage of being less invasive compared to a CSF biomarker, less costly than a PET scan, and more widely available and clinically easier to use compared to cortical atrophy measures (Chupin et al., 2009). However, using hippocampal volume in the clinical setting is less straightforward compared to the use of this measure in a research setting.

Hippocampal volume needs to be normalized by or adjusted for intracranial volume (ICV) (Whitwell et al., 2001) to control for intersubject (Barnes et al., 2010) and gender (Pintzka et al., 2015) variations in head size, as well as variation in head size estimations in serial scans (Whitwell et al., 2001). The most widely used method in neuroimaging research is adjustment for ICV using its inclusion as a covariate in regression analyses. A less commonly used normalization approach is dividing the hippocampal volume by another volume that can be accurately measured and is not significantly impacted by neurodegenerative processes, typically ICV. In this study, we investigate normalization by cerebellar volume (hippocampus to cerebellar volume ratio) as an alternative approach, to correct for head size/premorbid brain volume as the cerebellum has been shown to be little affected by age-related atrophy in the absence of clinical dementia. Neurodegeneration in AD gradually progresses from the medial temporal lobe to the parietal and frontal lobes and then to the posterior parts of the brain. The cerebellum is among the last brain regions affected by AD pathology (Thal et al., 2002). We have recently shown that cerebellar atrophy is not different in MCI compared to normal aging (Tabatabaei-Jafari et al., 2017). Furthermore, while cerebellar atrophy increases in AD, it remains lower in other regions and particularly in the medial temporal lobe (Tabatabaei-Jafari et al., 2017). Thus, using the cerebellum as a reference area should be both methodologically robust and practical in a clinical context. Importantly, regional brain volume is more accurately measured than ICV using semi-automated methods, such as FreeSurfer (Heinen et al., 2016), and unlike ICV also less affected by field strength (Heinen et al., 2016; Nordenskjold et al., 2013) and segmentation method (Hansen et al., 2015; Keihaninejad et al., 2010; Malone et al., 2015).

Although hippocampal volume is not sufficiently accurate to be clinically useful as a single predictor of MCI who progress to AD, it is a useful benchmark. If other measures sufficiently improve the predictive value of hippocampal volume, they may be worth for further consideration. The Mini–Mental State Examination (MMSE) may be a good candidate. A recent Cochrane review indicated that the weighted sensitivity and specificity of the MMSE for conversion from MCI to AD are 54% and 80% in a limited number of available studies (Arevalo-Rodriguez et al., 2015). Moreover, evidence suggests that a combination of cognitive measures and hippocampal volume can improve the predictive value of hippocampal volume for predicting AD conversion in MCI (Devanand et al., 2008). Therefore, such a combination is also likely to improve on the classification performance of hippocampal volume for identifying MCI who convert to AD in short term from all those who do not convert.

In the present study, we investigated the classification performance of MMSE and hippocampal volume normalized by cerebellar volume or ICV both individually and in combination, to identify individuals with MCI who will convert to AD within 5 years. We expected that these combinations of measures would have classification accuracies high enough to be useful in clinical practice.

2. Methodology

2.1. Study participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by a principal investigator, Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

A total of 1289 participants with MCI (n = 872) or CN (n = 417) at baseline were considered for inclusion. All MCI participants who were stable for at least 6 months after baseline and converted to AD or reverted to CN within 5 years (confirmed with 2 consecutive stable diagnoses) or were stable for at least 5 years were included. Participants who were CN at baseline and were stable throughout the study were also included.

Based on diagnosis and diagnostic change, participants were categorized into 4 groups: (1) MCIc (N = 187), MCI patients who converted to AD in less than 5 years; (2) MCIs (N = 112), MCI patients who were stable for 5 years or more; (3) MCIr (N = 39), MCI patients who reverted to CN in less than 5 years; and (4) CN (N = 322), patients who remained cognitively healthy for the whole follow-up period.

Details of the diagnostic criteria can be found at the ADNI web site (http://www.adni-info.org/Scientists/AboutADNI.aspx). Briefly, participants were classified as CN if they had an MMSE greater than 24, had a clinical dementia rating (CDR) of 0, and did not meet diagnostic criteria for MCI, dementia, or depression. Participants were classified as MCI if they had an MMSE greater than 24, had a CDR of 0.5, had a subjective report of memory concern, had an objective memory loss, had preserved daily living activity, and did not meet diagnostic criteria for dementia. AD participants have MMSE scores less than 26, have a CDR of 0.5 or 1.0, and fulfill criteria for clinically probable AD according to the Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.

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