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Cognitive variability—A marker for incident MCI and AD: An analysis for the Alzheimer's Disease Neuroimaging Initiative

Eric D. Anderson[a,*], Michelle Wahoske[b,c], Mary Huber[a], Derek Norton[d], Zhanhai Li[d], Rebecca L. Koscik[e], Emre Umucu[f], Sterling C. Johnson[b,c,e,g], Jana Jones[h], Sanjay Asthana[b,c,g], Carey E. Gleason[b,c,g,**], for the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Human Services, School of Education and Human Services, Wright State University, Dayton, OH, USA*
[b]*Division of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*
[c]*Wisconsin Alzheimer's Disease Research Center, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA*
[d]*Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA*
[e]*Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*
[f]*Department of Rehabilitation Psychology and Special Education, School of Education, University of Wisconsin, Madison, WI, USA*
[g]*Geriatric Research, Education and Clinical Center, William S. Middleton Memorial Veterans Hospital, Madison, WI, USA*
[h]*Department of Neurology, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA*

Abstract

Introduction: The potential of intra-individual cognitive variability (IICV) to predict incident mild cognitive impairment (MCI) or Alzheimer's disease (AD) was examined and compared to well-established neuroimaging and genetic predictors.

Methods: IICV was estimated using four neuropsychological measures for $n = 1324$ Alzheimer's Disease Neuroimaging Initiative (ADNI) participants who were cognitively healthy or diagnosed with MCI at baseline. IICV was used to predict time to incident MCI or AD, and compared to hippocampal volume loss and *APOE* ε4 status via survival analysis.

Results: In survival analyses, controlling for age, education, baseline diagonosis, and *APOE* ε4 status, likelihood ratio tests indicate that IICV is associated with time to cognitive status change in the full sample ($P < .0001$), and when the sample was restricted to individuals with MCI at baseline ($P < .0001$).

Discussion: These findings suggest IICV may be a low-cost, noninvasive alternative to traditional AD biomarkers.

Keywords: Cognitive variability; Cognitive biomarker; Biomarker; Alzheimer's disease; Mild cognitive impairment; MCI; Alzheimer's disease neuroimaging initiative; ADNI

1. Introduction

The prevalence of Alzheimer's disease (AD) is rising, creating an urgency to develop effective interventions [1,2]. Current strategies include: (1) intervention during the protracted presymptomatic or preclinical stages; and (2) development of practical and effective means to prevent the disease-associated suffering and untenable costs. A prevention-focused approach necessitates the identification of biological indicators of disease process, that is, biomarkers [3,4].

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.

*Corresponding author. Tel: +1-937-775-4208; Fax: +1-937-775-2042.

**Corresponding author. Tel: +1-608-280-7000; Fax: +1-608-280-7230.

E-mail address: eric.anderson@wright.edu (E.D.A.), ceg@medicine.wisc.edu (C.E.G.)

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Major efforts, including the Alzheimer's Disease Neuroimaging Initiative [5] (ADNI) and the Australian Imaging, Biomarkers and Lifestyle [6] (AIBL) Study of Aging, have expanded our understanding of preclinical and subclinical stages of AD and what biomarkers might be used to detect disease processes well before the onset of clinical symptoms. The most promising biomarkers are obtained from cerebrospinal fluid and brain imaging [7]. However, given the difficulties in disseminating collection methods outside of research centers, and the arduous and invasive nature of some collection procedures, there is a desire to develop noninvasive, convenient markers [8,9]. The development of a cognitive marker, once established and validated, would offer an alternative for individuals unable or unwilling to submit to the collection of traditional biomarkers.

One such proposed cognitive marker, intra-individual cognitive variability (IICV), estimates variability between cognitive domains measured at one time-point. Overall, researchers have used two conceptual methods to investigate the prognostic value of cognitive variability. The first method being an examination of variability across domains at one time (dispersion) [10–14], and the second being variability across trials (inconsistency) administered either in one session or over time [15–20] or both dispersion and inconsistency [17,19].

Holtzer et al. [10] and many others [13,14,20] have examined the usefulness of a dispersion-based IICV to predict cognitive decline and incident AD. This approach is not new. For example, significant disparity between verbal and performance intelligence quotients (IQs) is a long-established correlate with underlying neuropathology [21,22]. In Holtzer et al. [10], IICV was estimated as the degree to which an individual's test scores differed from their mean standardized test performance. The investigators found greater variability in performance (dispersion) was associated with increased risk for dementia a decade later. This suggested IICV, like traditional biomarkers, might co-occur with preclinical brain alterations.

We hypothesized that IICV would predict incident AD and mild cognitive impairment (MCI), and that IICV would demonstrate strong criterion validity, estimated by comparing IICV with an established neuroimaging biomarker, hippocampal volume loss (HVL), and with apolipoprotein ε4 allele (*APOE* ε4) a genetic risk marker. Our overall goal was to explore the utility of IICV as a potential marker of preclinical cognitive changes and examine whether baseline IICV predicted subsequent incident cognitive endpoints, including MCI and AD.

2. Methods

2.1. Study design

Using an ex-post facto design and using an estimate of IICV used by Holtzer et al. [10] as our primary predictor, we examined the association of IICV and conversion to MCI or AD in an ADNI sample, including adults who were cognitively healthy or diagnosed with MCI at baseline. We repeated our analyses with an MCI sub-sample. Finally, we examined the contribution of IICV as a predictor of incident MCI and AD when HVL and a genetic risk factor, *APOE* ε4 status, were also included in the models.

2.2. ADNI

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by PI Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD (adni-info.org [23]).

2.3. Participants

Data were collected at ADNI study centers and clinics across the United States and Canada from three ADNI funding cycles (ADNI 1, ADNI 2, and ADNI GO) [5,24,25]. ADNI eligibility criteria included the following: age 55 to 90 years; English or Spanish language speakers; no diagnosis of depression; and baseline diagnosis of early AD, MCI, or cognitively normal (CN). Cognitive status was confirmed with designated cut off scores for the Clinical Dementia Rating Scale, mini-mental state examination, and Wechsler Memory Scale Logical Memory II. A complete account of ADNI exclusion criteria can be found at www.adni-info.org [23]. Evaluations were repeated every 6 months (ranging from 6 to 72 months), with a mean total follow-up time of 30.81 months (SD = 23.85). The results of cognitive assessments, physical examinations, and MRI scans were considered in determining diagnostic status [24,25]. Supplementary Material describes how our primary outcome, diagnostic conversion was determined.

Before application of exclusion criteria in our study, the total subject pool included 1729 participants. We excluded subjects if they completed fewer than two visits, had incomplete or missing neuropsychological data, or carried a diagnosis of AD at baseline. After exclusionary criteria were applied, 1324 participants remained in the sample (see Fig. 1). For the MCI subgroup analyses, individuals who were CN at baseline were excluded, resulting in a sample of 825 individuals.

2.4. Estimate of cognitive variability

We sampled the following cognitive domains to determine IICV: Attention, processing speed, executive functioning, working memory, and verbal memory. In total, four index scores from three tests were used to calculate participants' IICV score. Specific indices included: Rey