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Sensitivity of composite scores to amyloid burden in preclinical Alzheimer's disease: Introducing the Z-scores of Attention, Verbal fluency, and Episodic memory for Nondemented older adults composite score

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Abstract

Introduction: Cognitive composite scores developed for preclinical Alzheimer's disease (AD) often consist of multiple cognitive domains as they may provide greater sensitivity to detect β-amyloid (Aβ)–related cognitive decline than episodic memory (EM) composite scores alone. However, this has never been empirically tested. We compared the rate of cognitive decline associated with high Aβ (Aβ+) and very high Aβ (Aβ++) in cognitively normal (CN) older adults on three multidomain cognitive composite scores and one single-domain (EM) composite score.

Methods: CN older adults (n = 423) underwent Aβ neuroimaging and completed neuropsychological assessments at baseline, and at 18-, 36-, 54-, and 72-month follow-ups. Four cognitive composite scores were computed: the ADCS-PACC (ADCS-Preclinical Alzheimer Cognitive Composite), ADCS-PACC without the inclusion of the mini-mental state examination (MMSE), an EM composite, and the Z-scores of Attention, Verbal fluency, and Episodic memory for Nondemented older adults (ZAVEN) composite.

Results: Compared with Aβ+ CN older adults, Aβ++ CN older adults showed faster rates of decline across all cognitive composites, with the largest decline observed for ZAVEN composite (d = 1.07). Similarly, compared with Aβ− CN older adults, Aβ+ CN older adults also showed faster rates of cognitive decline, but only for the ADCS-PACC no MMSE (d = 0.43), EM (d = 0.53), and ZAVEN (d = 0.50) composites.

Discussion: Aβ-related cognitive decline is best detected using validated neuropsychological instruments. Removal of the MMSE from the ADCS-PACC and replacing it with a test of executive

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function (verbal fluency; i.e., the ZAVEN) rendered this composite more sensitive even in detecting Aβ-related cognitive decline between Aβ+ and Aβ++ CN older adults.

Keywords: Preclinical Alzheimer's disease; Cognitive composite; Amyloid; Cognitive decline; Neuropsychological assessment

1. Introduction

There is now consensus that in cognitively normal (CN) older adults, high levels of β-amyloid (Aβ), assessed using Aβ imaging or cerebrospinal fluid sampling, represent the preclinical stage of Alzheimer's disease (AD) [1–3]. Multiple prospective studies have shown that substantial decline in cognitive function occurs in Aβ+ CN older adults over periods of 6–54 months, even in the absence of any progression to clinically recognizable mild cognitive impairment (MCI) or AD [4–7]. In Aβ+ CN older adults, this cognitive decline is associated with faster accumulation of Aβ [1,8] as well as greater loss of hippocampal volume and decreased levels of brain metabolism [9,10]. Although there is general agreement that Aβ levels should be classified as low (Aβ−) or high (Aβ+) [11,12], a recent analysis from our group using a two-graph receiver operator curve (ROC) analysis of Aβ levels in the Australian Imaging, Biomarkers, and Lifestyle (AIBL) cohort indicated that a standardized uptake value ratio (SUVR) of 1.9 provided the optimal cut point for distinction of Aβ levels in people with dementia from age-matched healthy controls [2]. Hence, when Aβ levels in CN older adults were classified additionally as being high (Aβ+: SUVR 1.50–1.90) or very high (Aβ++: SUVR >1.90), only Aβ++ CN individuals showed increased rates of cognitive decline relative to Aβ− CN older adults. In fact, CN older adults with Aβ+ did not show cognitive decline over a 36-month period [5]. Furthermore, in CN older adults, Aβ++ was associated with a higher risk of progression to MCI or AD compared with CN adults with Aβ+ [2]. Taken together, these data suggest that it may be prudent to consider Aβ burden beyond a single positive/negative category in the design of clinical trials for new anti-Aβ therapies [13,14].

An important consideration in measuring the effects of Aβ in clinical research studies and clinical trials of preclinical AD is the method used to operationalize a cognitive end point. Currently, there is consensus that the composite measures used commonly to characterize disease progression in patients with prodromal AD or dementia, such as the mini-mental status examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), or the clinical dementia rating (CDR) scale, are not appropriate for use in CN older adults because data distributions from these scales are characterized by restricted range of possible scores, ceiling effects, and negative skew, thus rendering it insensitive to subtle changes [15–17]. As such, research into cognitive decline in preclinical AD uses composite outcome measures based on data from standardized neuropsychological tests, such as tests of episodic memory and executive function, on which performance is most affected in this early disease stage [5,18,19].

Multiple studies from different natural history cohorts indicate that in preclinical AD, episodic memory provides a highly reliable and sensitive index of Aβ-related cognitive decline [3–5,20]. Therefore, episodic memory (EM) composite scores provide a sound comparator for determining the extent to which newer composite measures based on tests that measure cognitive domains other than episodic memory can yield any improved sensitivity of Aβ-related cognitive decline. Some composite scores developed for preclinical AD include measures of additional cognitive domains on the basis that their inclusion may provide greater sensitivity to detect Aβ-related cognitive decline than EM composite scores alone [21]. For example, the recently validated cognitive composite for the Anti-Amyloid treatment in Asymptomatic Alzheimer's disease (A4) trial, the Alzheimer Disease Cooperative Study (ADCS) Preclinical Alzheimer Cognitive Composite (ADCS-PACC), emphasized measurement of specific cognitive domains, rather than specifying the tests used to operationally define those domains. The ADCS-PACC combines measures of episodic memory (e.g., measures of list learning such as the Free and Cued Selective Reminding Test [FCSRT] or the California Verbal Learning Test, Second Edition [CVLT-II] and measures of paragraph recall such as the Wechsler Memory Scale Logical Memory delayed recall [LM-DR] or New York University Paragraph Recall test), complex attention (e.g., the Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test [DSST] score), and a general cognitive screen (e.g., the MMSE total score) [18]. Although each of the tests used to define episodic memory and complex attention in the ADCS-PACC have demonstrated sensitivity to cognitive decline in early AD, the MMSE has not [16,17]. Therefore, its inclusion may reduce the sensitivity of the ADCS-PACC because of its suboptimal metric characteristics when its use is restricted to CN older adults (i.e., ceiling effects, negative skew, poor test-retest reliability) [15–17].

An additional limitation of the ADCS-PACC is that it does not include a measure of executive function when substantial Aβ-related decline in this domain is also observed reliably in preclinical AD, often to a greater extent than