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Certified normal: Alzheimer's disease biomarkers and normative estimates of cognitive functioning

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ABSTRACT

Normative samples drawn from older populations may unintentionally include individuals with preclinical Alzheimer's disease (AD) pathology, resulting in reduced means, increased variability, and overestimation of age effects on cognitive performance. A total of 264 cognitively normal (Clinical Dementia Rating = 0) older adults were classified as biomarker negative ("Robust Normal," n = 177) or biomarker positive ("Preclinical Alzheimer's Disease" [PCAD], n = 87) based on amyloid imaging, cerebrospinal fluid biomarkers, and hippocampal volumes. PCAD participants performed worse than robust normals on nearly all cognitive measures. Removing PCAD participants from the normative sample yielded higher means and less variability on episodic memory, visuospatial ability, and executive functioning measures. These results were more pronounced in participants aged 75 years and older. Notably, removing PCAD participants from the sample significantly reduced age effects across all cognitive domains. Applying norms from the robust normal sample to a separate cohort did not improve Clinical Dementia Rating classification when using standard deviation cutoff scores. Overall, removing individuals with biomarker evidence of preclinical AD improves normative sample quality and substantially reduces age effects on cognitive performance but provides no substantive benefit for diagnostic classifications.

1. Introduction

As the era of Alzheimer's disease (AD) secondary prevention trials begins, there is increased interest in detecting the earliest cognitive changes in the course of the disease. A decline in cognitive functioning is unquestionably the most face valid indicator of AD progression, but accurately capturing the earliest declines is dependent on several factors, including the psychometric characteristics of the cognitive tests used and the quality of the normative sample used as a reference group. Cognitive measures must have adequate reliability and validity and should be sensitive and specific to healthy versus diseased states. At an individual level, capturing changes in cognitive performance is best accomplished by comparing current test performance with prior assessments. When these data are not available, a useful approach is to compare test performance to that of healthy persons of a similar demographic profile. Detecting cognitive decline in this situation is highly dependent on the normative sample used as a basis for comparison. Thus, reference groups used to provide normative values should be composed of individuals who are comparable to the individuals being tested in terms of ages, education levels, and premorbid functioning. Participants in normative samples should also be carefully screened for health conditions that may impact cognitive performance. Yet, despite efforts to produce healthy normative

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samples, a substantial portion of included individuals may have subtle declines in cognitive performance due to undetected underlying disease (Sliwinski et al., 1996; Storandt and Morris, 2010). Most neurodegenerative diseases have a "preclinical" phase in which the disease process is underway in the brain, but the degree of pathology is not sufficient to produce overt clinical symptoms (Foltynie, 2003; Price and Morris, 1999). In older populations, as much as 30%–40% of individuals over the age of 65 years may be in a preclinical stage of AD (Price et al., 2009).

The pathological hallmarks of AD can be quantified in vivo using cerebrospinal fluid (CSF) assays and neuroimaging methods such as positron emission tomography (PET) and structural and functional magnetic resonance imaging (MRI). CSF biomarkers including amyloid-β_{1-42} ($A\beta_{1-42}$), total tau (t-tau) and phosphorylated tau_{181} ($p\text{-}tau_{181}$), and neuroimaging markers including [^{11}C] Pittsburgh compound B (PIB) PET and hippocampal volume, have been used to describe the course of the preclinical stages of AD (Bateman et al., 2012; Knopman et al., 2012; Vos et al., 2013). Results from these studies have consistently shown that AD pathology may begin well before overt symptoms of dementia are present. β-Amyloidosis begins at least 10–20 years before clinical diagnosis, followed by tau aggregation into neurofibrillary tangles resulting in neuronal injury (Bateman et al., 2012; Jack et al., 2013; Sperling et al., 2011; Villemagne et al., 2013). The final proposed preclinical stage of AD is characterized by "subtle cognitive decline"; however, this has yet to be fully operationalized (Sperling et al., 2011). Studies that have modeled cognitive trajectories in the preclinical stage of AD have shown cognitive declines beginning within approximately 7–10 years of clinical diagnosis (Grober et al., 2008; Roe et al., 2013; Saxton et al., 2004), with a pronounced acceleration 3–5 years before diagnosis (Howieson et al., 2008; Johnson et al., 2009). Because the preclinical stage of AD is defined by the absence of clinically significant cognitive and functional impairment, conventional normative samples do not exclude individuals with preclinical AD, and therefore, may be less sensitive to detecting subtle impairments in cognitive functioning (Sliwinski et al., 1996; Storandt and Morris, 2010).

Sliwinski et al. (1996) demonstrated that failing to screen for preclinical AD cases has three primary influences on normative data. First, individuals with preclinical disease tend to have slightly worse performance, resulting in normative data with reduced mean scores. Second, variability in cognitive performance is more pronounced in preclinical AD, resulting in normative data with larger standard deviations and skewed distributions. Finally, since there is a strong correlation between dementia risk and age, the influence of age on cognitive performance is magnified, especially in older age ranges where the prevalence of preclinical AD is much higher. Several investigators have since attempted to improve on conventional normative data by using methods to identify individuals in the preclinical stage of AD and exclude them from normative samples. Most existing studies have applied a "longitudinal" exclusion criterion wherein individuals that have been followed for several years and progressed to dementia are selectively removed from normative samples, ostensibly resulting in a more robust normative data set. The longitudinal method has consistently produced normative data sets with higher mean scores, reduced variability, and less influence of age on cognitive test performance (De Santi et al., 2008; Pedraza et al., 2010; Ritchie et al., 2007; Sliwinski et al., 1996; Storandt and Morris, 2010). However, the clinical utility of the longitudinal method has been unclear. Some studies have reported improved diagnostic classification accuracy using robust normative data (De Santi et al., 2008; Holtzer et al., 2008), whereas others have not (Ritchie et al., 2007; Storandt and Morris, 2010). One possible reason why these studies have demonstrated mixed results could be that the longitudinal method relies solely on clinical diagnosis of dementia, and therefore excludes only persons in the later preclinical stages or those with more a more rapid course of progression. Thus, there is a risk that a large percentage of individuals who did not progress to a clinically symptomatic stage of dementia during the study follow-up period may indeed have AD pathology that is affecting their cognitive performance.

The purpose of this study was to determine if the identification and subsequent removal of individuals who are cognitively normal, but exhibit biomarker evidence of preclinical AD pathology, would improve normative cognitive data and show better correspondence with the Clinical Dementia Rating (CDR; Morris, 1993). To this end, we selected cognitively normal participants from ongoing studies of normal aging and dementia who had completed biomarker studies. Participants were classified according to our previously published cutoff values for AD biomarkers as belonging to a biomarker-positive group with Preclinical Alzheimer's Disease pathology (PCAD) or a biomarker-negative group of "Robust Normals." We hypothesized that removing participants with PCAD would increase mean scores, decrease variability, normalize distributions, and reduce age effects compared to a conventional normative sample that included participants with PCAD. We also hypothesized that application of the robust norms to a separate cohort of longitudinally followed participants would improve correspondence with CDR classification accuracy when standard deviation cutoff scores were used.

2. Methods

2.1. Participants

Participants were older adult volunteers enrolled in ongoing studies of aging and dementia at the Knight Alzheimer's Disease Research Center (KADRC) at the Washington University School of Medicine. Inclusion and/or exclusion criteria and assessment methodology have been detailed in previous publications (Berg et al., 1998; Coats and Morris, 2005). KADRC participants were living independently in the community at study entry and underwent annual clinical assessment unless prevented by death, illness, refusal, or relocation from the greater St. Louis area. Each participant and their collateral source, a close friend, or family member were interviewed with standard instruments with respect to cognitive and functional abilities (Morris et al., 2006) and that information was used by experienced physicians and nurse-clinicians to determine the CDR (Morris, 1993). The Human Research Protection Office at Washington University School of Medicine approved the KADRC studies, including the Healthy Aging and Senile Dementia Study (P01AG003991), the Alzheimer's Disease Research Center study (P50AG05681), and the Antecedent Biomarkers for AD: the Adult Children Study (P01AG026276). Written informed consent was obtained from all participants at enrollment.

2.1.1. Normative samples

Participants for the normative samples (Fig. 1) were selected from the larger KADRC cohort based on the following criteria: completion of baseline cognitive assessment; CDR score of 0 at all available visits; at least one annual follow-up assessment; at least 65 years of age at baseline; completion of lumbar puncture (for CSF biomarkers) within 18 months of baseline or completion of PIB PET within 18 months of baseline; and structural MRI within 18 months of baseline.

2.1.2. Longitudinal sample

Participants for the longitudinal sample (Fig. 1) were selected from the larger KADRC cohort based on the following criteria: CDR 0 at study entry and completed at least two follow-up clinical and cognitive assessments; at least 65 years of age at baseline. Participants in the longitudinal sample were further classified as