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A comparison of theoretical and statistically derived indices for predicting cognitive decline

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Abstract

Background: Both theoretical and statistically derived approaches have been used in research settings for predicting cognitive decline.

Methods: Fifty-eight cognitively normal (NC) and 71 mild cognitive impairment (MCI) subjects completed a comprehensive cognitive battery for up to 5 years of follow-up. Composite indices of cognitive function were derived using a classic theoretical approach and exploratory factor analysis (EFA). Cognitive variables comprising each factor were averaged to form the EFA composite indices. Logistic regression was used to investigate whether these cognitive composites can reliably predict cognitive outcomes.

Results: Neither method predicted decline in NC. The theoretical memory, executive, attention, and language composites and the EFA-derived "attention/executive" and "verbal memory" composites were significant predictors of decline in MCI. The best models achieved an area under the curve of 0.94 in MCI.

Conclusions: The theoretical and the statistically derived cognitive composite approaches are useful in predicting decline in MCI but not in NC.

Keywords: Alzheimer's disease; AD; Factor analysis; Neuropsychological test; Mild cognitive impairment; MCI; Cognitive decline; Memory decline; Executive decline; Conversion; Progression; Prognosis

1. Introduction

Mild cognitive impairment (MCI) is a risk state for dementia [1]. Patients with MCI invariably manifest more cognitive difficulties than one might expect given their age but can still live independently [1], thus failing to meet the diagnostic criteria for dementia [2,3]. Although an estimated 15% of people living with MCI progress to dementia each year [4], some remain stable or even revert to exhibit normal cognition [5]. Early identification of cognitively normal (NC) individuals who will convert to MCI and MCI individuals who will convert to dementia with confidence and high sensitivity will provide the opportunity to intervene at early stages and have greater potential for modifying the disease course.

Neuropsychological (NP) testing is an essential tool for assessing cognitive function in both the prodromal and

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dementia stages [6–8]. It has been previously shown that NP testing can capture areas of cognitive decline relatively early in the disease course [9–11]. NP testing can effectively capture areas of cognitive decline before the observation of any clinical symptoms [12]. NP evaluations obtained in the prodromal stages predicted Alzheimer's disease (AD) pathology with 89% accuracy, as later confirmed by autopsy [13].

Comprehensive NP batteries often comprised different measures that tap into various cognitive domains. The common practice is to derive composite scores (i.e., domains) with a normalized distribution that can be more easily compared with one another [14]. Traditionally, the tests that comprise these domains have been chosen on a theoretical basis. Individual test results are grouped and interpreted in theoretically derived cognitive domains, such as attention, language, memory, visuospatial, and executive functions. For example, measures that require recall are often included in the memory domain and measures that require concentration are often included in the attention domain.

Theoretically derived cognitive domains can be used to predict future cognitive decline [14–17]. The memory domain has been suggested to discriminate best between NC and MCI, and be most predictive of progression to AD [8,12,18,19]. Free recall, recognition memory, and paired-associate learning have been shown to be prominently impaired in patients with AD and MCI [8,12,20]. One study showed that memory assessment predicted diagnosis of normal cognition and dementia with 94.5% and 66.7% accuracy, respectively, in a large cohort of older adults [21]. Welsh et al. demonstrated that the amount of information recalled after a 10-minute delay on the Consortium to Establish a Registry for AD [22] differentiated MCI [16,23] from healthy normal controls with >90% accuracy [24]. These studies demonstrate that NP assessments that track deficits in the memory domain help detect symptom markers essential for early diagnosis.

Executive functions in everyday life, such as planning a vacation or creating a grocery list, are often affected early in the disease course. Such decline is reflected in executive deficits in NP testing [25,26]. Performance in the executive domain is highly predictive of future conversion from MCI to AD [14,15,27]. The executive domain includes tests that require planning and organization. The decision whether to include measures into the theoretical executive domain as opposed to the attention domain is driven by the additional need to formulate a plan of goal-directed action or to inhibit an overlearned response. Notably, some executive tests require problem-solving skills rather than just processing speed and concentration [25,28]. The Wisconsin Card Sorting Test-64 [29], a novel problem solving measure, and the Stroop tests [30], a measurement of response inhibition, are therefore typically categorized as executive functioning tasks and aid in the prediction of future cognitive decline [31].

NP test groupings can also be derived using statistical methods [6,7,14,32–36]. Such methods have been shown to have high accuracy, specificity, and sensitivity in diagnosing dementia [6,32,34]. By combining individual test scores into composite scores using multivariate techniques, diagnoses are less prone to errors caused by chance and the minimum amount of tests needed to detect cognitive decline decreases [14]. Exploratory factor analysis (EFA) is a widely used technique that is commonly used to identify the internal relationships among variables and to create interpretable composite scores from large sets of variables. When compared with the theoretical model, where each of the constituent parts are analyzed separately, composite scores in EFA may be more powerful, in that they may increase measurement precision, help avoid specific characteristics of a particular test that may be influenced by chance, and limit the number of statistical tests needed to derive a conclusion [14]. This method groups specific tests within a domain when these tests are highly intercorrelated (i.e., have high covariance), ensuring that they tap the same cognitive constructs. The decision of how to group tests is thus based on the data rather than on theory [37]. When NP tests are run through EFA and the resulting factor models are produced, incorrectly classified models that demonstrate a negative error variance can also be revised and compared with better models [34]. This is important in analyzing and confirming the best model comprising the most accurate factors. Previous studies of EFA with NP tests have yielded different groupings of tests than the theoretical model [6,34,38]. Yet, EFA has been shown to accurately predict cognitive decline in older adults and to improve diagnostic classification and predict cognitive decline [6,32,34,38].

In two large EFA studies, one using data from the National Alzheimer's Coordinating Center (N = 12,020) [6] and the other using data from the Alzheimer's Disease Neuroimaging Initiative (N = 819) [7], a five-factor solution was found to be stable over time and within diagnostic groups. In these studies, Hayden et al. [6] derived a four-factor solution including memory, executive function, language, and attention composites, whereas Park et al. [7] also included a fifth visuospatial factor. Another EFA study of 1288 middle-aged adults with and without family risk factors for AD derived a different five-factor model comprising verbal ability, visuospatial, speed and executive function, working memory, and verbal and memory factors that was able to explain 63% of the cognitive variance. These factors were invariant across groups defined by age, gender, family history of AD, and ApoE4 genotype [34]. Taken together, these data-driven analytic studies suggest that cognition is similarly organized across the geriatric cognitive spectrum and that factor scores resulting from these cognitive domains can be used stably across all groups. The aforementioned studies also suggest that EFA can effectively differentiate unique aspects of samples that are relevant, given that different factors emerged across different cohorts. These group differences would