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Featured Article

A composite measure of cognitive and functional progression in Alzheimer's disease: Design of the Capturing Changes in Cognition study

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Abstract

Introduction: Cognitive testing in Alzheimer's disease (AD) is essential for establishing diagnosis, monitoring progression, and evaluating treatments. Assessments should ideally be brief, reliable, valid, and reflect clinically meaningful changes. There is a lack of instruments that meet all these criteria. In the Capturing Changes in Cognition (Catch-Cog) study, we seek to correct these deficiencies through the development and validation of a composite measure combining cognition and function: the cognitive-functional composite (CFC). We expect that the CFC is able to detect clinically relevant changes over time in early dementia stages of AD.

Methods/Design: We will include patients (n = 350) with mild cognitive impairment or mild dementia due to AD from memory clinics in the Netherlands and the United Kingdom. We will include cognitively healthy volunteers (n = 30) as a control group. The CFC is based on the "cognitive composite" and the Amsterdam instrumental activities of daily living questionnaire. We will investigate test–retest reliability with baseline and 2- to 3-week follow-up assessments (n = 50 patients and n = 30 healthy controls). We will involve experts and participants to evaluate the initial feasibility and refine the CFC if needed. Subsequently, we will perform a longitudinal construct validation study in a prospective cohort (n = 300) with baseline, 3-, 6-, and 12-month follow-up assessments. The main outcome is cognitive and functional progression measured by the CFC. Reference measures for progression include traditional cognitive and functional tests, disease burden measures, and brain imaging methods. Using linear mixed modeling, we will investigate longitudinal changes on the CFC and relate these to the reference measures. Using linear regression analyses, we will evaluate the influence of possible confounders such as age, gender, and education on the CFC.

Discussion: By performing an independent longitudinal construct validation, the Catch-Cog study of the novel CFC will contribute to the improvement of disease monitoring and treatment evaluation in early dementia stages of AD.

Keywords: Alzheimer's disease; Cognition; Composite measure; Daily function; Longitudinal construct validation; Mild cognitive impairment; Prospective cohort

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1. Background

Assessing cognition in Alzheimer's disease (AD) is essential for establishing diagnosis, monitoring progression, and evaluating treatments [1,2]. Commonly used cognitive tests have shown adequate quality for diagnostic use [3,4]. However, the quality of these tests for the measurement of changes over time remains questionable [5].

One limitation is the duration of cognitive assessment, which can take up to several hours. This can be burdensome for patients and result in fatigue and loss of concentration. These factors add to measurement error and may be a reason for patients to abort the testing procedure [6]. A European Task Force suggested that measuring progression in mild AD should focus on the domains that are vulnerable for decline, specifically episodic memory (EM), working memory (WM), and executive functioning (EF) [7]. A benefit of this specificity is more concise testing.

A variety of tests are available for the previously specified domains [8]. However, most of these are unable to detect changes over time in mild cognitive impairment (MCI) and mild AD [9]. For example, mixed results are found for the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog), a test battery frequently used to evaluate therapies in AD [10]. Previous studies have demonstrated that most ADAS-Cog subtests suffer from either floor or ceiling effects in MCI and mild AD, which strongly limits their sensitivity to changes over time [11–13]. However, there is also evidence that some parts show good responsiveness in these disease stages [14,15]. Potentially sensitive tests for EF originate from the Neuropsychological Test Battery (NTB) [16]. Based on existing data on the ADAS-Cog and NTB, Harrison et al. selected three EM tests and two EF tests with a total administration time of 20 minutes. First results showed this "cognitive composite" (CC) to be a concise and reliable measure in mild AD [17].

Although cognitive performance is an important predictor of everyday life performance, test scores only explain part of the variance in functional status, which limits their clinical relevance [18]. Informant reports measuring "instrumental activities of daily living" (IADL) may complement cognitive assessments to provide a clinically meaningful change [19]. IADL are cognitively complex everyday activities, such as cooking and managing finances [20]. Unfortunately, the psychometric quality of most existing IADL instruments is questionable or unknown [21,22]. Recent promising developments include the Amsterdam IADL Questionnaire© (A-IADL-Q): an informant-based measure with good psychometric properties regarding reliability, validity, responsiveness, and diagnostic accuracy in early dementia [23–26]. The A-IADL-Q is now incorporated in the European Prevention of Alzheimer's Dementia study given its potential capacity to measure functional changes in preclinical and prodromal AD [27].

Combining sensitive cognitive and functional tests into a single composite measure may yield a useful tool to detect clinically relevant changes over time in MCI and mild AD [28]. This is highly relevant for symptomatic and disease-modifying trials, in which treatments are tested that aim to improve cognition and function [7]. Previous studies have proposed composite measures as endpoints for longitudinal changes. Most of these involve cognitive tests only [29–31] or address global function without focusing on specific activities of daily living [32], which hampers their clinical relevance. Furthermore, they are designed using retrospective data sets and thus need further validation in independent cohorts. An independently validated measure to detect clinically meaningful changes over time in MCI and mild AD is thus still lacking. Therefore, the "Capturing Changes in Cognition" (Catch-Cog) study has been designed. We aim to develop and validate a short composite measure combining cognition and function: the cognitive-functional composite (CFC). The CFC is based on preparatory work on the CC and A-IADL-Q. We expect that the CFC is able to detect changes over time in MCI and mild AD and that these changes relate to clinical and biological measures associated with disease progression.

2. Methods and design

2.1. Study participants

We will include patients ($n = 350$) with MCI or mild AD. They will be recruited via outpatient memory clinics from (1) the VU University Medical Center (VUmc) Alzheimer Center, Amsterdam, The Netherlands ($n = 140$); (2) the Alzheimer Center Rotterdam, The Netherlands ($n = 50$); (3) the University Medical Center Groningen (UMCG), The Netherlands ($n = 60$); and (4) the Brain Health Clinic at the University of Edinburgh, United Kingdom ($n = 100$). Before inclusion, participants have undergone a dementia assessment in their center, including medical history, neurological and neuropsychological examination, and brain imaging. Diagnoses are made according to the National Institution on Aging criteria [1,33], in a multidisciplinary diagnostic meeting including at least a neurologist or psychiatrist with neuropsychology input. To ensure mild AD, we will include people with a Mini–Mental State Examination (MMSE) score $\geq$18 [34]. Other inclusion criteria include age $\geq$50; sufficient proficiency of the study language; and availability of a study partner. Exclusion criteria address potential confounders for cognitive and functional decline, specifically presence of another significant neurological or psychiatric disorder; Geriatric Depression Scale score $\geq$6 [35]; and current abuse of alcohol or drugs. We will also exclude people who participate in a clinical trial within our follow-up time frame, to avoid potential practice effects due to repeated cognitive testing.

In the VUmc Alzheimer Center, we will additionally include cognitively healthy participants ($n = 30$) as a control group. They will be recruited from an existing database containing healthy volunteers. Before enrollment, all