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A novel cognitive-functional composite measure to detect changes in early Alzheimer's disease: Test–retest reliability and feasibility

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Abstract

Introduction: To improve the detection of changes in Alzheimer's disease, we designed the cognitive-functional composite (CFC). As a first validation step, we investigated its test–retest reliability and feasibility of use.

Methods: We performed a test–retest study with 2–3 weeks between assessments, including patients with mild cognitive impairment or mild Alzheimer's disease dementia and cognitively healthy participants. We calculated intraclass correlation coefficients type absolute agreement for all CFC measures and compared baseline and retest scores using paired sample *t*-tests. We evaluated feasibility by interviewing participants.

Results: Forty-three patients (40% female, mean age = 69.9) and 30 controls (50% female, mean age = 65) were included. Subtest intraclass correlation coefficients ranged from .70 to .96. We found negligible improvements after retesting on only two subtests. Overall, patients perceived the administration of the CFC as feasible.

Conclusions: The CFC is a stable and feasible measure in mild cognitive impairment and mild Alzheimer's disease, and thereby meets important quality metrics for clinically meaningful outcome measures.

Keywords: Activities of daily living; Alzheimer's disease; Cognition; Feasibility; Test–retest reliability; Outcome measures

1. Background

Neurodegenerative diseases leading to dementia are characterized by progressive cognitive decline and increasing interference in daily functions [1]. Alzheimer's disease (AD), which is the main cause of dementia worldwide, is a continuum starting with a preclinical phase in which pathology develops but clinical symptoms are still absent [2]. It can be accompanied by subjective complaints as the first signal of the disease [3,4]. Cognitive deficits become more prominent in the prodromal phase of mild cognitive impairment (MCI) [5] and are ultimately severe enough to interfere with daily life in the dementia stage [6]. Measuring cognition and everyday function across the AD continuum is pivotal for monitoring clinical progression and evaluating both symptomatic relief and disease-modifying therapies.

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Currently used cognitive and functional measures have shown to be of insufficient quality for these purposes, due to their insensitivity to clinically meaningful changes over time [7]. For example, widely used tests such as the Mini–Mental State Examination [8] and the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) [9] have been shown to be inappropriate for use in the design and evaluation of clinical trials targeted at MCI and mild AD [10–13]. As to the measurement of everyday functioning, recent reviews pointed out that most commonly used questionnaires are only of limited use to detect the early functional decline [14,15].

Consequently, many researchers have expressed the need for an improved measure that is capable of detecting clinically meaningful changes in MCI and mild AD [16,17]. To this end, the "Capturing Changes in Cognition" project was initiated [18]. Based on preparatory work [19,20] and input from patients and experts, we designed a novel composite assessment combining measures of cognition and function: the "cognitive-functional composite" (CFC) [18]. The CFC comprises existing cognitive tests focusing on the domains that are known to be vulnerable to decline in incipient AD, specifically episodic memory, working memory, and executive functioning (EF) [17]. To amplify its clinical relevance, the CFC encompasses an everyday functioning questionnaire focusing on instrumental activities of daily living (IADL) [20,21]. IADL are activities that require the use of multiple cognitive processes and include activities such as cooking, driving, and managing finances. Difficulties in IADL performance are among the earliest clinical symptoms in MCI and early AD dementia [15,22].

The present study reports on the first validation step of the novel CFC, in which we focused on its stability and feasibility. First, we investigated test–retest reliability of the CFC subtests. Second, we examined the influence of potential practice effects on the cognitive parts. Practice effects are improvements in cognitive test performance that may result from repeated exposure [23]. They are a potential threat for longitudinal cognitive assessment, as they can result in either underestimation of actual cognitive decline or overestimation of real treatment effects [24]. It is therefore important to explore the presence of practice effects on novel outcome measures designed for longitudinal use, such as the CFC. Previous studies on the presence of practice effects on cognitive tests in individuals with and without cognitive impairment have shown contrasting results [23–27]. Consequently, we explored potential practice effects on the CFC subtests separately for individuals with MCI or mild AD dementia and cognitively healthy individuals. Third, we computed an overall CFC score including all subtests. We investigated whether this score was influenced by age or education, and we examined the stability of this score in both groups. Finally, we evaluated feasibility of the CFC, with a focus on patients' experiences with respect to its administration time, modality, and perceived burden.

2. Methods

2.1. Study design

This study is a multicenter, observational, prospective cohort study, conducted at three Dutch sites and one United Kingdom site. We used a test–retest design with 2–3 weeks between assessments. Data were collected between November 2015 and November 2016. The Medical Ethical Committee of the VU University Medical Center (VUmc) approved the study for all Dutch centers. The South East Scotland Research Ethics Committee approved the study for the United Kingdom site. All participants and study partners gave written informed consent.

2.2. Participants

We included patients with a clinical diagnosis of MCI or probable AD dementia (n = 48) and cognitively healthy participants (n = 30) with their study partners. Patients were recruited via the VUmc Alzheimer Center Amsterdam, the Spaarne Gasthuis Haarlem, the Alzheimer Center Rotterdam, the University Medical Center Groningen, and the Centre for Dementia Prevention at the University of Edinburgh. Before inclusion in the present study, all patients had undergone a screening assessment including medical history, neurological, and neuropsychological examination in their center. Diagnoses were made in a multidisciplinary meeting containing at least a neurologist, psychiatrist, or geriatrician and with neuropsychology input. MCI and probable AD were diagnosed according to the corresponding National Institute of Aging-Alzheimer's Association core clinical criteria [5,6]. Biomarkers (structural brain imaging or cerebrospinal fluid) were available for most but not all patients and were used to increase or decrease the likelihood of AD according to McKhann et al [6]. If not available, we relied on the clinical diagnosis of MCI and AD. Other inclusion criteria were as follows: (1) Mini–Mental State Examination score $\geq$ 18 [8]; (2) age $\geq$ 50; and (3) availability of a study partner (i.e. a spouse, relative, or close friend) who was capable and willing to participate. Exclusion criteria were as follows: (1) neurological or psychiatric diagnoses other than AD (Geriatric Depression Scale score $\geq$ 6 [28]); (2) current or a history of substance abuse; or (3) participation in a clinical trial during the timeframe of the present study.

Cognitively healthy participants originated from an existing healthy volunteer database from the VUmc Alzheimer Center. Eligible participants had (1) an age $\geq$ 50; (2) neuropsychological test results within age- and education-adjusted norms; and (3) an available study partner.

2.3. Materials

The CFC was designed by the Capturing Changes in Cognition working group [18]. It comprises seven existing, validated cognitive tests. Three episodic memory tests