INTRODUCTION

General background

Dementia is a clinical syndrome characterized by progressive cognitive decline leading to increased interference in everyday functioning and, ultimately, complete functional dependence [1]. It was estimated that a number of 50 million people were suffering from dementia worldwide in 2018 (World Alzheimer Report, 2018). In the Netherlands, approximately 270.00 people had a dementia diagnosis in 2018 (Alzheimer Nederland factsheet, 2018). It is expected that these numbers will double in the next 20 years, as the world population is growing older, and therefore more at-risk for developing dementia, and there is no cure available yet (World Alzheimer Report, 2018). The total estimated healthcare costs of dementia were $1 trillion dollars last year, and these costs will increase even more quickly than its prevalence resulting in a huge challenge for national health systems (World Health Organization, 2018). As such, dementia is not only a burden for those living with dementia and their cares, but it also has a major impact on society as a whole.

Dementia can be caused by several neurodegenerative diseases, with Alzheimer’s disease (AD) being the most common cause as it accounts for ~70% of all dementia diagnoses. AD pathology is thought to develop years before the onset of overt dementia, resulting in gradual increasing severity of clinical symptoms that usually start with memory impairment and executive dysfunction [2]. The clinical course of AD is thought to start with a preclinical stage that might be accompanied with perceived subjective cognitive decline (SCD) [3, 4], followed by a prodromal stage of mild cognitive impairment (MCI) in which cognitive impairment can be objectified using standardized cognitive testing [5]. The moment when cognitive impairment causes severe interference with everyday life activities is often marked as transition to the dementia stage [6]. The hypothesized clinical trajectory of AD is visualized in Figure 1 [4], illustrating that emerging cognitive decline induces increased impairment in everyday functioning.

Figure 1.
Hypothesized trajectory of decline in cognition and activities of daily living (ADL) along the continuum of AD (Figure adapted from Sperling et al. 2011).
Capturing clinical progression: current challenges and needs

Capturing changes in cognition and everyday functioning along the AD trajectory is essential for monitoring clinical progression and the evaluation of treatments. In both research and clinical practice, cognitive performance is usually measured using a neuropsychological assessment. Such an assessment typically comprises different individual neuropsychological tests assessing a variety of cognitive domains, including, but not limited to, episodic memory, semantic memory, attention, language and executive functioning (EF) [7]. Commonly used neuropsychological tests have shown adequate diagnostic accuracy for MCI and dementia due to AD [8]. However, the quality of these neuropsychological test for the measurement of disease progression is questionable, especially in the pre-dementia stages SCD and MCI, and mild dementia [9-11].

Quality limitations for the measurement of progression include the duration of neuropsychological testing, which can take up to several hours. Therefore, tests scores may be affected by fatigue effects, or the investigation may be experienced as too burdensome causing participants to abort the testing procedure and avoid further follow-up testing [12]. Second, it has been repeatedly shown that widely applied tests show floor or ceiling effects in scoring, especially in MCI and mild dementia stages [9, 13-15]. This is probably due to the fact that these tests were initially designed to assess changes in more severe stages of dementia, and do not focus on cognitive domains that are prone to decline in earlier clinical stages of the disease [16]. As such, patients undergo extensive and inadequate neuropsychological testing. Finally, neuropsychological test scores do not fully translate to everyday life performance, thereby limiting the clinical relevance of these scores [17, 18].

To know whether cognitive disorders interfere in everyday life, questionnaires aimed at ‘activities of daily living’ (ADL) are often used [19]. However, several challenges for existing functional measures are encountered for the detection of clinically relevant changes in dementia. For example, existing ADL questionnaires have been criticized with respect to their content, as they focus on basic ADLs that are less prone to cognitive decline in MCI and early stages of dementia [20] (Figure 1). In addition, most widely-applied questionnaires are outdated as they do not feature items indexing contemporary functional activities such as online purchasing and self-organized travel arrangement [20, 21]. Moreover, the responsiveness of ADL instruments has received limited attention, as have other crucial psychometric properties such as reliability and validity [20, 22].

To summarize, quality limitations of cognitive and functional measures that are currently considered ‘gold standards’ for clinical progression mainly concern their validity and sensitivity to change over time (Table 1). These deficiencies
hamper the understanding of the disease course, as well as the evaluation of treatment effects in therapeutic trials aimed at early stages of AD. Therefore, researchers and clinicians have addressed the need for a measure that is capable of detecting clinically relevant changes in early stages of AD [23]. Ideally, such a measure would be brief, so as to avoid fatigue effects, and focus on the cognitive domains and activities that are prone to decline in early disease stages [16]. Furthermore, it should provide a reliable and valid score of cognitive performance and be free of range restrictions to support its sensitivity to change over time (Table 1).

### Table 1. Challenges and needs of outcome measures for clinical progression.

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long administration time</td>
<td>Brief but comprehensive</td>
</tr>
<tr>
<td>Include irrelevant cognitive domains and activities of daily living</td>
<td>Focus on relevant cognitive domains and complex activities of daily living</td>
</tr>
<tr>
<td>Show floor- and ceiling effects</td>
<td>No range restrictions in scoring</td>
</tr>
<tr>
<td>Clinical meaningfulness uncertain</td>
<td>Captures clinically meaningful changes</td>
</tr>
</tbody>
</table>

### The Capturing Changes in Cognition (Catch-Cog) project

To fulfill the need for a clinically relevant measure that is sensitive to change over time in MCI and early dementia, we designed the Capturing Changes in Cognition (Catch-Cog) project. The overall aim of this project was to design and validate a composite measure consisting of both neuropsychological tests and an everyday functioning part, that could provide a useful measure of clinical progression. The design of this composite was inspired by preparatory work on a short cognitive test battery to assess change in MCI and mild dementia due to AD [24, 25], and the recently developed Amsterdam Instrumental Activities of Daily Living (IADL) Questionnaire [26, 27].

The cognitive test battery as proposed by Harrison et al. includes a selection of five existing cognitive tests focusing on episodic memory and EF, which were individually shown to be capable of detecting change in a retrospective dataset including mild AD dementia participants [24]. The Amsterdam IADL Questionnaire is an informant-based questionnaire that was designed to improve the measurement of IADL in incipient dementia [26]. It was developed with input from clinicians, patients and caregivers, and includes more relevant and modern IADL activities as compared to traditional questionnaires. Previous studies have demonstrated the good psychometric qualities of the Amsterdam
IADL Questionnaire is, with respect to content validity, reliability, validity, responsiveness and diagnostic accuracy in dementia [27-29].

The rationale behind combining these cognitive and functional measures into one composite score is that it could summarize complex measures of cognition and everyday function and thereby provide a suitable measure of clinical progression. Preparatory work on both the cognitive tests and Amsterdam IADL Questionnaire have provided evidence that they are suitable for this purpose, but they have not yet been validated as a single measurement instrument in an independent, prospective cohort. An independent validation of a novel outcome measure is needed to enhance its future implementation in research and clinical practice, as also emphasized by regulatory agencies such as the Food and Drug Administration [30] and European Medicines Agency [31]. The goal of the Catch-Cog project was therefore to perform a longitudinal construct validation of our novel composite measure, in a prospective cohort including individuals on the clinical spectrum from SCD to dementia.

General aim and thesis outline

The general aim of this thesis was to extend the knowledge on the measurement of clinical progression in AD. Our first objective was to investigate whether the novel cognitive-functional composite (CFC) is a suitable measure for clinical progression in MCI and mild dementia. As such, the majority of chapters in this thesis focus on the different validation steps that were taken in the Catch-Cog study (Figure 2). Next to that, we aimed to provide more insight on whether optimal cognitive outcomes to assess clinical changes would differ at different clinical stages within the AD spectrum.

Figure 2. Overview of the key questions of the Catch-Cog study addressed in this thesis.
We aimed to achieve our aims by addressing the following research questions:
- Is the CFC focused on relevant aspects of cognition and function?
- Does the CFC provide a reliable measure of cognition and function?
- Does the CFC capture clinically relevant aspects of disease severity?
- Is the CFC sensitive to change over time?
- To what extent do cognitive outcomes to assess changes differ at different clinical stages within the AD spectrum?

Part 2 addresses the first research question. In chapter 2.1 we describe the rationale and design of the Catch-Cog study, as well as the background on the cognitive and functional components that are included in the CFC. In chapter 2.2 we aimed to develop and validate a shortened version of the Amsterdam IADL Questionnaire, in order to provide a more concise and user-friendly measure of functional decline to include in the CFC.

Part 3 addresses the second and third research questions. In chapter 3.1 we report the test-retest reliability of the CFC and the results of our evaluation of its feasibility, with a focus on patients' experiences with respect to its administration time, modality and perceived burden. In chapter 3.2, we investigated whether the Amsterdam IADL Questionnaire captures functional impairment that is associated with the underlying neurobiology of AD, in order to further support the construct validity of the Amsterdam IADL Questionnaire. In chapter 3.3, we performed a cross-sectional psychometric evaluation of the CFC using baseline data of the Catch-Cog study cohort. We evaluated several measurement properties of the CFC including its construct validity, clinical relevance and suitability for the target population, and compared the CFC to traditional clinical endpoints that are considered the current gold standards of progression.

Part 4 addresses the fourth and fifth research questions. In chapter 4.1 we investigated the sensitivity to change of the CFC over a period of one year in individuals across the clinical spectrum from SCD to dementia. We again performed a head-to-head comparison between the CFC and current gold standards of progression, to investigate whether the CFC offers advantages over the use of other clinical endpoints as a single, primary outcome measure of disease progression. In chapter 4.2 we investigated the sensitivity of existing cognitive tests within different clinical stages of AD as defined in the National Institute on Aging and Alzheimer's Association research framework 2018.

The main findings of this thesis are summarized in Part 5, followed by a discussion of the results as well as recommendations for future research.
References


7. Lezak, M.D., Neuropsychological assessment. 2004: Oxford University Press, USA.


14. Duke Han, S., et al., Detectable


29. Sikkes, S.A., et al., Assessment of instrumental activities of daily living in dementia: diagnostic value of the Amsterdam Instrumental Activities

Introduction 15
