Differential diagnosis in the memory clinic: Exploring the value of improved neuropsychological examination
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Citation for published version (APA):

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CHAPTER 1
GENERAL INTRODUCTION

1.1. BACKGROUND
The population is rapidly ageing. Between 2000 and 2050, the proportion of the world's population over 60 years will double from about 11% to 22%. By 2050 the world will have almost 400 million people aged 80 years and more (WHO, 2012a). In the Netherlands in 2012 16% of the total population was over 65 years of age. In 2060, it is expected that 26% will be 65 years or older. Ten percent will be 80-plus (Centraal Bureau voor de Statistiek, http://statline.cbs.nl). The ageing of the world's population is an indicator of improving global health. However, ageing will also present challenges. Old age is the primary risk factor for dementia and cognitive decline. It is estimated that 25-30% of people aged 85 or older are having some degree of cognitive impairment and even 50% of people aged around 100 (Nelson et al., 2011). Currently, the number of people living with dementia worldwide is estimated at 35.6 million. This number will double by 2030 and more than triple by 2050 (WHO, 2012b). The same trend is observed in the Netherlands where it is estimated that currently 256,000 people are suffering from dementia and that this number will double by 2040 (Alzheimer Nederland, www.alzheimer-nederland.nl/extra/deltaplan-dementie.aspx). The high costs of the disease will challenge health systems to deal with the predicted future increase of cases. The costs are assessed at US$ 604 billion per year at present and are expected to increase even more quickly than the prevalence of dementia (WHO, 2012b). In the Netherlands around 5% of the total health care costs is consumed by dementia, which makes it the disease with the highest costs. Due to the future increase of cases, care costs will increase with on average 2.7% per year (Alzheimer Nederland, www.alzheimer-nederland.nl/extra/deltaplan-dementie.aspx).

At present, a treatment to cure dementia or to alter its progressive course is not available. However, once medication will become available, these drugs will be most effective when prescribed in the earliest (prodromal) stage of the dementia process (Ewers, Sperling, Klunk, Weiner, & Hampel, 2011; Nestor, Scheltens, & Hodges, 2004; Sperling et al., 2011). Yet, especially in the prodromal stages of dementia, the differential diagnosis of mental complaints that may signify an early stage of dementia is difficult. One reason for this difficulty is that the transition between normal cognitive aging and cognitive im-
pairment due to degenerative cerebral disease is a gradual one. A second great challenge in diagnosing preclinical dementia is the inter-individual variability among older adults, both in intellectual function at a given age and in rates of decline over time (Ganguli, 2014). Third, there is frequent co-occurrence of cognitive impairment and emotional-behavioral or psychiatric symptoms. Estimates of this co-occurrence in pre-dementia patients vary from 25% in population-based studies to more than 60% in clinical samples (Steffens et al., 2006). This causes frequent misclassification of pre-dementia and functional psychiatric states in elderly patients. In the future we will therefore need valid means to distinguish between patients who will and who will not progress to dementia, and consequently to distinguish who may and who may not benefit from drugs. Of course, this implies that we will have to be able also to determine the syndrome’s aetiology in the individual patient (Dubois & Albert, 2004).

1.2. THE PRODROMAL STAGE OF DEMENTIA
The first symptoms of degenerative brain diseases that ultimately lead to dementia most often concern memory impairment (Arnáiz, & Almkvist, 2003; Bäckman, Jones, Berger, Laukka, & Small, 2004; Hodges, 1998; Grober, Lipton, Hall, & Crystal, 2000; Weintraub, Wicklund, & Salmon, 2012). However, also subtle problems in other cognitive domains like mild word finding problems, difficulties in finding one’s way in an unknown environment, and inability to perform complex tasks such as managing one’s finances can be symptomatic of an early dementia stage (Bäckman et al. 2004; Brown, Devanand, Liu, & Caccappolo, 2011). Other early signs of dementia are neuropsychiatric rather than cognitive, such as lack of interest in one’s surroundings, inactivity, and emotional flattening (Feldman et al., 2004; Geda et al., 2008; Lopez, Becker, & Sweet, 2005; Lyketsos et al., 2002; Lyketsos et al., 2011). These emotional signs may easily be mistaken as symptoms of depression. During the course of the disease these early symptoms gradually become more conspicuous until they affect the daily life of the patients to such a degree that a diagnosis of dementia is inevitable (Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011). The transitional stage between normal aging and dementia is nowadays mostly called “mild cognitive impairment” (MCI; Flicker, Ferris, & Reisberg, 1991; Petersen et al. 1999; Petersen, 2011).

1.3. MILD COGNITIVE IMPAIRMENT
While it is clear that there exists a transitional stage between normal aging and clinical dementia, it has been a matter of debate how to describe and define it. Since the early
sixties of the last century, many concepts have been proposed, for example 'benign senescent forgetfulness' (Kral, 1962), 'age-associated memory impairment' (Crook, Bahar, & Sudilovsky, 1987), and 'cognitive decline, no dementia' (Eibly, Hogan, & Parhad, 1995). In the past two decades, the concept of MCI (Flicker et al., 1991; Petersen, 2011) has received much attention. The exact criteria of MCI are still under discussion, but most researchers and clinicians define MCI as subjective complaints of cognitive dysfunction (preferably confirmed by an informant), evidence of cognitive impairment as demonstrated by neuropsychological tests, preserved general cognitive function, intact activities of daily living and no dementia (Albert et al., 2011; Dubois & Albert, 2004; Petersen et al., 1999; Petersen et al., 2001; Petersen, 2004; Winblad et al., 2004). In the newly released fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), the American Psychiatric Association has introduced the term mild Neurocognitive Disorder (NCD) for the MCI concept. In 2003, an international working group expanded the concept of MCI and proposed subgroups based on patterns of cognitive impairment (Petersen, 2004; Winblad et al., 2004). This classification system broadly differentiates MCI into subgroups of amnestic and non-amnestic according to whether the patient has memory impairment or not, and both subtypes can be further classified as single or multiple domain based on the number of cognitive domains affected. Furthermore, emotional and neuropsychiatric symptoms such as depression, apathy and irritability, are present in about 50% of MCI patients (Feldman et al., 2004; Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004; Lopez et al., 2005; Lyketsos et al., 2002).

1.4. PROGNOSTIC VALUE OF MCI

It has been shown in a large number of population-based and clinical studies that patients who satisfy MCI criteria are at high risk of developing dementia. If amnestic symptoms are involved, conversion rates from MCI to Alzheimer’s disease are about 10-15% per year. Approximately 80% show progression to dementia within six years (Petersen et al., 2001; Petersen, 2007). Patients with non-memory MCI or multiple domains MCI may also convert to other types of dementia such as vascular dementia, fronto-temporal dementia or dementia with Lewy bodies (Dubois et al., 2007; Gauthier et al., 2006; Petersen et al., 2001). Thus, previous findings show that the conversion rate of MCI to dementia greatly exceeds the risk of conversion in healthy-age matched controls. These impressive conversion rates, however, have been observed in selected samples of relatively uncomplicated patients. In a broader context, the association between MCI and AD is far from unidirectional. Some patients do not progress to
Differential diagnosis in the memory clinic: dementia at the long term, and some patients even return to normal upon re-examination (Maioli et al., 2007; Mitchell & Shiri-Feshki, 2009; Visser, Kester, Jolles, & Verhey, 2006). Although these patients satisfied the MCI criteria at baseline, a diagnosis of MCI in the sense of a pre-dementia stage is inaccurate because their temporary cognitive decline was probably not due to a degenerative brain disease.

1.5. WHY IS EARLY DIAGNOSIS IMPORTANT?
Accurate diagnosis of dementia symptoms due to AD (and other dementias) in the earliest possible stage is important for several reasons. First, early and accurate diagnosis may aid in providing adequate patient care as soon as it is needed. As mentioned above, once (disease-arresting) drugs become available, early and accurate diagnosis will even be more critical, because quality of life is to be preserved early in the disease process (Nestor et al., 2004). Second, even in the absence of effective drugs, it still is important to distinguish early stages of degenerative brain diseases from other conditions that give rise to mental complaints. After all, many of these other conditions are treatable by means we have already at our disposal. When somatic diseases are concerned, it is the task of physicians, in particular neurologists and geriatricians, to diagnose and treat them. When non-organic emotional or behavioral problems, or psychiatric diseases are concerned, psychotherapy or psychiatric treatment may be indicated. Adequate health care requires early diagnosis to utilize these treatment options. A third reason why correct early diagnosis is important has to do with efficiency of research efforts. As mentioned above, the prognostic value of MCI is not perfect. This implies that subjects who suffer from other conditions than degenerative brain disease may contaminate samples of MCI patients in research projects on early dementia. Such false positive MCI diagnoses may obscure the relationships under study, and may complicate the testing of hypotheses. Last but not least, many patients and relatives ask for an early diagnosis. Alzheimer’s disease and dementia in general have received much attention in the lay press during the last decades. This has resulted in a trend for patients and relatives to present themselves in an early stage to clinics in case of mental complaints. Moreover, many of today’s emancipated patients are no longer satisfied with provisional answers or a let’s-wait-and-see attitude, but want their doctors to draw clear diagnostic and prognostic conclusions.
1.6. DEFINING THE PROBLEM

1.6.1. Highly selective samples of MCI patients
As mentioned before, there is frequent co-occurrence of cognitive impairment and emotional-behavioral or psychiatric symptoms, which may cause misclassification of pre-dementia and functional psychiatric states in elderly patients (Steffens et al., 2006). However, there is a lack of research that takes this co-occurrence into account (Steffens et al., 2006). Dementia researchers often evade this problem by excluding patients with psychiatric disorders. Most studies on pre-dementia stages have been performed in highly selective samples of MCI patients with isolated cognitive impairments or with patients who fulfilled strict MCI criteria predictive for the development of dementia. This methodological strictness is appropriate from a scientific point of view, but it does not reflect clinical practice, and thus limits the generalizability of these findings to the larger population visiting memory clinics. Furthermore, the border between MCI and dementia may be a conceptually sharp line, but in clinical reality it is a rather fluid transition zone, largely depending on clinical judgment of functional status (Forlenza, Diniz, Stella, Teixera, & Gattaz, 2013; Gomar et al. 2011; Morris, 2012). Similarly, there is no clearly defined border between normal aging and MCI either (Loewenstein et al., 2012). Thus, the research practice to split off a strictly defined MCI category from the spectrum of cognitive impairments in memory clinic populations is somewhat artificial. This thesis explicitly addresses the co-occurrence of cognitive and emotional-behavioural symptoms by means of including patients with mild psychiatric co-morbidity for whom the differential diagnosis included a possible early stage of dementia. People who appeared to be ‘worried well’ were not excluded either. They were patients who were cognitively normal, did not have cognitive test scores in the impaired range, and who did not meet criteria for a psychiatric disorder. Although they had cognitive complaints and were unsure about their mental stats, these worries appeared to be unjustified.

1.6.2. Underestimation of behavioral (neuropsychological) methods
The limited predictive validity of the MCI diagnosis has stimulated researchers to search extensively for biochemical, genetic and neuroimaging markers to improve the prediction of conversion to dementia (e.g., Allan, Sexton, Welchew, & Ebmeier, 2010; Chérelat et al., 2012; Drago et al., 2011; Hansson et al., 2006; Karas et al., 2004; Thurfjell et al., 2012). For example, to date, considerable research effort is being invested to find or improve neurochemical biomarkers of dementia, especially β-amyloid peptide 42
Differential diagnosis in the memory clinic: (Aβ42) and elevated levels of tau protein in cerebrospinal fluid (CSF) (Blennow & Zettenberg, 2013; Forlenza, Diniz, & Gattaz, 2010). Neuroimaging methods to visualize the accumulation of amyloid and tau in brain tissue are developing rapidly (Jack, & Holtzman, 2013), and are beginning to enter clinical diagnostic routine. This trend is also reflected in the most recently developed set of criteria for the symptomatic predementia phase of AD for use in research settings, which incorporate biomarkers based on imaging and CSF measures (Albert et al., 2011). Although these measures are promising, they are not suitable yet to be used in routine clinical care, given the current lack of standardization among the techniques and the uncertainty regarding the optimal cutoff points for identifying high-risk groups (Forlenza et al., 2010; Petersen, 2011). Furthermore, the CSF biomarkers are informative in relatively young patients, but they lose much of their diagnostic potential in older patients (Bouwman et al. 2009; Schmand, Huizinga, & van Gool, 2010), who are the vast majority of dementia patients. Finally, it is questionable if such biomarkers will ever be able to accurately mark the appearance of clinical symptoms of dementia, since these symptoms are of a behavioral nature. Therefore, for the accurate early assessment of symptoms of dementia, behavioral methods will always be of vital importance.

The behavioral test methods, however, based on which MCI and similar diagnoses are made, are not infallible. This imperfection is probably an important reason why the predictive validity of MCI is limited. However, the flaws of behavioral methods seem to be taken for granted by most dementia researchers. This is unfortunate because improvement of these methods is very well possible, and should be pursued before other more expensive or invasive techniques are called for.

1.6.3. Non-credible performance
Until now, the limited predictive validity of the MCI diagnosis has been related mainly to differences in research methods (diagnostic criteria, type of cohort) or to several reversible causes of cognitive decline (such as psychiatric conditions, and a variety of metabolic, nutritional or sensory impairments) (Gauthier & Touchon, 2005). Little attention has been paid to another cause: invalidity of the diagnosis due to non-credible performance during neuropsychological evaluation. Non-credible performance is a threat to the validity of neuropsychological test results (Bush et al., 2005). If patients are unable or unwilling to invest the required amount of effort while doing the tests, abnormal test results may not validly reflect cognitive impairments due to cerebral dysfunction. In other words, it has become uncertain whether the tests measure what they intend to measure,
i.e. cognitive functioning or cognitive impairment. Symptom validity testing may detect this lack of validity.

A symptom validity test (SVT) is a test that in the layman's eye appears to measure a cognitive function, for example memory, whereas in reality it measures mental effort (Bianchini, Mathias, & Greve, 2001; Rogers, 2008). SVTs are widely used in forensic psychology to detect malingering. However, also other influences than right-out malingering may result in abnormal performance on SVTs. Healthy volunteers 'fail' on these tests when they are instructed to feign memory impairment (e.g., Brockhaus & Merten, 2004; Iverson, Green, & Gervais, 1999; Jing, Slick, Strauss, & Hultsch, 2002). Moreover, compensation-seeking individuals were shown to suppress their performance on SVTs (e.g., Green, Lees-Haley, & Allen, 2002).

If abnormal test results of patients who fail SVTs are indeed not reflecting cognitive impairments due to brain disease, we may assume that MCI patients with genuine cognitive impairments as confirmed by credible performance on SVTs are likely to convert to dementia, irrespective of psychiatric co-morbidity. On the other hand, in MCI patients with non-credible SVT performance, abnormal cognitive test scores cannot validly be interpreted as signs of genuine impairments, and a degenerative brain disease is much less likely, although not ruled out.

1.7. GENERAL AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to improve the neuropsychological assessment of symptoms that precede dementia, and consequently, to improve the prediction of conversion to dementia in participants for whom the differential diagnosis included a possible early stage of dementia, irrespective of mild psychiatric co-morbidity. More specifically, the aim of our studies is twofold.

First, we performed two preparatory studies expanding the research on the employability of SVTs frequently used in clinical practice. In chapter 2 we sought to investigate the equivalence of the English and Dutch versions of the Word Memory Test (WMT; Green, 2003), one of the most popular symptom validity tests currently available. Furthermore, we examined the demographic characteristics that may influence performance, in order to create a demographically corrected normative data set. Chapter 3 focuses on providing further evidence for the specificity of several effort tests by investigating whether children (whose cognitive skills are not yet fully developed) can pass these SVTs.

Second, we aimed at examining brain-behavior relationships and neuropsychological profiles as a function of credible and non-credible performance. For this pur-
Differential diagnosis in the memory clinic: we recruited patients (N=170) from the neurological and geriatric outpatient clinics, day clinics and memory clinics of several general and psychiatric hospitals in Amsterdam and surrounding area, the Netherlands. Patients between 50 and 85 years of age were included if they presented with a) complaints of decline in cognitive or behavioral functioning (as expressed by the patient or a close relative) not normal for age, and b) essentially intact instrumental activities of daily living. To improve the representativeness of this sample for clinical practice, psychiatric (co)-morbidities, like major depressive disorder, common anxiety disorder or adjustment disorder, was not an exclusion criterion. People who appeared to be ‘worried well’ were not excluded either. The main exclusion criterion for our sample was a clear dementia syndrome that could be diagnosed by a dementia specialist without detailed neuropsychological assessment. Thus, the study sample was a naturalistic patient mix that is representative for first visitors of memory clinics, with a broad spectrum of cognitive functioning and impairments ranging from worried well to MCI and early dementia cases. Chapter 4 describes the findings of a study examining the associations between hippocampal volume and memory performance as a function of SVT results. In chapter 5, we sought to identify the cerebral morphometric correlates of neuropsychological deficits in the part of our large, heterogeneous sample of elderly patients showing credible performance. In chapter 6 finally, we focus on the neuropsychological characterization of patients showing a pattern of test scores indicative of genuine amnesia on the WMT, the so-called ‘dementia-profile’, to verify if this profile indeed reflects genuine memory impairment.

In chapter 7 we summarize the findings and implications of our study. Furthermore, caveats of the studies described in this thesis, as well as directions for future studies will be discussed.

References
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