Differential diagnosis in the memory clinic: Exploring the value of improved neuropsychological examination

Rienstra, A.

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CHAPTER 7
SUMMARY AND GENERAL DISCUSSION

7.1. GENERAL AIM
The overall objective of the studies described in this thesis was 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. The study sample was a naturalistic patient mix that consisted of first visitors of memory clinics, with a broad spectrum of cognitive functioning and impairments, ranging from 'worried well' to MCI and early dementia cases, as well as patients with mild psychiatric co-morbidity for whom the differential diagnosis included a possible early stage of dementia. 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 et al., 2013; Morris, 2012). Similarly, there is no clearly defined border between normal aging and MCI either. 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. Therefore, contrary to most previous studies, we employed a study sample that is representative for first visitors of memory clinics.

Specifically, the aims of our studies were to 1) expand the research on the employability of symptom validity tests (SVTs) in memory clinic populations, and 2) examine brain-behavior relationships as a function of credible and non-credible performance in our large, heterogeneous sample of elderly patients referred to memory clinics. In this final chapter we summarize and discuss the results of the studies presented in this thesis. We will address methodological aspects of the present research. Furthermore, the relevance and implications of the present findings for clinical practice and scientific research will be considered. We conclude with some recommendations for future research.

7.2. PREPARATORY STUDIES EXPANDING THE RESEARCH ON THE EMPLOYABILITY OF SVTS

7.2.1. Reference data for the Word Memory Test
The Word Memory Test (WMT; Green, 2003) is a word list-learning task containing multiple subtests, of which the first two are specifically designed to evaluate effort,
while the remaining subtests are conventional tests of verbal memory. Many studies have investigated the utility of the WMT as a symptom validity test (Brockhaus & Merten, 2004; Iverson et al., 1999; Jing, Slick, Strauss, & Hultsch, 2002). However, there is a lack of research presenting reference data for the conventional memory subtests of this task (Strauss, Sherman, & Spreen, 2006). In Chapter 2 we therefore examined the demographic characteristics that may influence performance on these memory subtests, in order to develop demographically corrected reference data. For this purpose, we administered the Dutch version of the WMT to 115 healthy Dutch controls. We compared their data to those of a Canadian group of healthy volunteers, and we demonstrated the equivalence of the English and Dutch language versions of the WMT. As expected, analyses of the combined Canadian and Dutch samples \((N = 155)\) showed that the memory scores declined with increasing age. Also, participants with lower levels of education performed worse than more highly educated subjects (Rienstra, Spaan, & Schmand, 2009). With this study we thus expanded the existing sample of adult normal controls and presented reference data stratified by age and level of education for use in research and clinical settings.

7.2.2. Validation of symptom validity tests using a ‘child-model’ of adult cognitive impairments

Chapter 3 aimed to provide further evidence for the specificity of several effort tests that are frequently used in clinical practice. Validation studies of SVTs in children are uncommon. However, since children’s cognitive abilities are not yet fully developed, their performance may provide additional support for the validity of these measures in adult populations. In other words, if it can be shown that the immature cognitive abilities of young children do not interfere with performance on SVTs, then this would provide evidence in support of the assumption that effort measures are relatively insensitive to mild cognitive disorders at an adult age (Rienstra, Spaan, & Schmand, 2010). We administered four SVTs, the Test of Memory Malingering (TOMM; Tombaugh, 1996), the WMT (Green, 2003), the Amsterdam Short Term Memory test (ASTM; Schmand & Lindeboom, 2004) and the Word Completion Memory Test (WCMT; Hilsabeck & LeCompte, 1997), along with several neuropsychological instruments to 48 Dutch school children aged 7 to 12. The results showed that children of early school age can easily pass the cut-off scores for sufficient effort of the TOMM and the WMT. They could pass the ASTM test if their reading skills were at a level equivalent to that of 9 year olds. All children passed our criterion of a negative WCMT score. However, the WCMT seems to be sensitive to level of verbal fluency (Rienstra et al., 2010). With
this study we thus provided additional support for the validity of three frequently used SVTs when applied in adult populations with mild cognitive impairments. For the WCMT, we concluded that mild cognitive impairments could interfere with passing the criterion for determining *deliberate* non-credible performance.

7.2.3. Discussion part I

The results of our study providing reference data for the WMT have enlarged the area of application of this test. Availability of appropriate reference values for the conventional memory subtests has two important advantages for the use of the WMT in clinical practice. First, improved reference data increase the efficiency of a neuropsychological evaluation since both effort quality and verbal memory can be investigated with a single test (Rienstra et al., 2009). In this respect, our study is innovative. The usual way to increase the efficiency of neuropsychological evaluation is exactly the opposite. Most previous studies with a similar aim were focused on ‘embedded measures’ that is, they evaluated suboptimal effort by defining clinically atypical patterns of performance for standard neuropsychological tests (e.g. Larrabee, 2003; Miele, Gunner, Lynch, & McCaffrey, 2012; Sherman, Boone, Lu, & Razani, 2002). We went off the beaten track by investigating effort with a symptom validity test, and expanding its function as a conventional memory test. A second advantage is that better reference data will lead to improved interpretation of the WMT profile of subtest scores (Rienstra et al., 2009). It has been shown that one way to differentiate non-credible responses from genuine memory impairment is to examine profiles of scores across subtests of different difficulty levels, in particular the difference between the effort subtests and conventional memory subtests (Green, Montijo, & Brockhaus, 2011; Howe, Anderson, Kaufman, Sachs, & Loring, 2007; Howe & Loring, 2009; Singhal, Green, Ashaye, Shankar and Gill, 2009). Therefore, appropriate reference data are of crucial importance to judge whether or not an individual’s profile is consistent with his age and education. This issue was further examined in Chapter 6.

Our validation study of SVTs in children has implications for the applicability of these effort measures in adult populations. The findings show that immature cognitive abilities do not interfere with performance on the TOMM and the WMT. Therefore we reasoned that these measures might be relatively insensitive to mild cognitive disorders at an adult age. Furthermore, these results support our choice of selecting especially these two SVTs for the use in our sample of patients for whom the differential diagnosis included a possible early stage of dementia. Although the findings suggest that reading ability significantly contributes to the ASTM test performance, all children older than
9 years passed the test. Thus, only some basic reading skills are required, which adults with schooling higher than grade 4 are expected to possess. The WCMT, as a test that has the potential to demonstrate that participants are deliberately exerting suboptimal effort, seemed a promising measure to find out whether participants are showing non-credible performance on purpose. However, since the results of our study showed that WCMT performance is probably related to immature (in children) or impaired (in adults) verbal fluency, the specificity of this test seems to be too low for use in patients with mild cognitive impairments. Therefore, whether non-credible performance in our patients results from a conscious attempt to suppress performance motivated by external incentives (i.e. malingering) is still an unanswered question.

7.3 BRAIN-BEHAVIOR RELATIONSHIPS AND NEUROPSYCHOLOGICAL PROFILES AS A FUNCTION OF CREDIBLE AND NON-CREDIBLE PERFORMANCE

7.3.1. Hippocampal-memory associations as a function of symptom validity

Although subjects with mild cognitive impairment (MCI) have an overall increased risk of developing dementia, the association is far from unidirectional. Some MCI patients remain stable for years or show full or partial recovery after initial cognitive abnormalities (Diniz, Nunes, Yassuda, & Forlenza, 2009; Maioli et al., 2007; Mitchell & Shiri-Feshki, 2006; Visser, Kester, Jolles, & Verhey, 2006). In such non-declining cases, abnormal neuropsychological test results may not validly reflect cognitive symptoms due to brain disease, and the usual brain-behavior relationships may be absent. In other words, it has become uncertain whether cognitive tests measure what they intend to measure, i.e. cognitive functioning or cognitive impairment. Symptom validity testing may detect this lack of validity (Rienstra et al., 2013). In Chapter 4 we examined symptom validity in our memory clinic sample, and its effect on the associations between hippocampal volume and memory performance. We hypothesized that if abnormal test results of patients who fail SVTs are indeed not reflecting cognitive impairments due to brain disease, brain–behavior relationships are weakened, or perhaps even completely absent, in these subjects. On the contrary, these associations would be quite strong in patients with credible SVT performance (Rienstra et al., 2013). Results showed that about seven percent of the patients scored positively on SVTs. However, only one of them was older than 65 years. Thus, this percentage was almost doubled in patients younger than 65 years of age. Furthermore, our study clearly showed that, as expected, the correlation between hippocampal volumes and memory performance in memory clinic patients was rather
strong. In our patients with non-credible SVT scores, associations between hippocampal volume and memory performance were negligible or absent, but they reported significantly more often symptoms of depression and anxiety (Rienstra et al., 2013). Thus, the data presented in this study confirm that brain-behavior relations may be obscured in patients who do not perform to the best of their ability during cognitive evaluation.

7.3.2. Cerebral morphometric correlates of neuropsychological deficits in patients who show credible performance

Previous studies investigating correlations between neuropsychological performance and brain atrophy in MCI patients have been performed in highly selective samples with isolated cognitive impairments or with patients who fulfilled strict MCI criteria predictive for the development of dementia (Rienstra et al., under revision). This methodological strictness is appropriate from a scientific point of view, but it does not reflect clinical reality, and thus limits the generalizability of these findings to the larger population visiting memory clinics. Furthermore, none of these studies analyzed a battery of neuropsychological tests tapping multiple cognitive domains in the same participants (Rienstra et al., under revision). Therefore, the aim of Chapter 5 was to identify the cerebral morphometric correlates of neuropsychological deficits in a naturalistic patient sample that is representative for first visitors of memory clinics, with a broad spectrum of cognitive functioning and impairments, excluding patients who showed non-credible performance. We used a comprehensive battery of neuropsychological tests, high-resolution magnetic resonance imaging (MRI), and a whole-brain voxel-based morphometry (VBM) analysis approach. The main finding of this study was that, across various cognitive functions, significant correlations with brain structure were found in about the same cerebral regions. These areas were located in several parts of the temporal lobe, in particular the bilateral middle temporal gyri. Moreover, our results indicate that cognitive function in non-memory domains is correlated with regional brain morphology outside the temporal lobes, but only when studied in isolation (Rienstra et al., under revision). More in particular, we found that associations with bilateral middle temporal lobe grey matter volume were not specific for various domains of cognitive functioning, but rather seemed to reflect a general relationship between volume loss and severity of cognitive impairments. Most correlations disappeared when they were adjusted for the influence of memory impairment. However, the primary memory impairment, characteristic for MCI patients, remained specifically related to lower volume of the left hippocampus, when variance in other cognitive domains was accounted for and even became more robust when adjusted for other cognitive (non-memory) impairments.
7.3.3. Neuropsychological characterization of patients with the WMT dementia profile

The aim of Chapter 6 was to investigate neuropsychological functioning in patients with a "dementia profile" on the WMT (Green, 2003). The dementia profile is used to reduce the number of false positive classifications (i.e. erroneously identifying a patient as exerting non-credible performance by a SVT while in fact he or she is giving abnormal, but valid responses due to truly impaired abilities) (Green, 2003). We hypothesized that, provided that the dementia profile reflects genuine memory impairment, corresponding cognitive deficits should be found in neuropsychological testing. Moreover, the profile might contribute to predicting dementia and cognitive decline with progression of time (Rienstra, Klein Twennaar, & Schmand, 2013). We divided participants into three groups according to their symptom validity performance at baseline: 1) people who passed the WMT effort subtests, thus showing credible performance, 2) people who failed the WMT easy subtests, but showed a dementia profile, and 3) people who failed the effort subtests but did not have a dementia profile, thus showing non-credible performance. We compared group results on an extensive neuropsychological test battery using the baseline and two-year longitudinal data. The results demonstrated that patients with the WMT dementia profile at baseline have a high chance of showing real cognitive impairment, and even more so two years later. They showed a faster cognitive decline than patients who passed the easy effort subtasks. Furthermore, our findings indicated that if a memory clinic patient has a WMT dementia profile, the clinician can be fairly confident that the patient is at least in a pre-dementia stage. Importantly, the non-credible performance group did not show cognitive decline after two years (Rienstra, Klein Twennaar, & Schmand, 2013). Thus, the data presented in this study show that the WMT dementia profile not only aids in the interpretation of the WMT results when it is utilized as a SVT, but also provides clinically relevant information on (future) cognitive impairment and early dementia.

7.3.4. Discussion part II

Taking an overall view of the findings in the second part of this thesis, we may formulate two main conclusions. First, non-credible cognitive test performance occurs in a non-negligible proportion of memory clinic patients, which, if undetected, will result in invalid MCI diagnoses. Second, brain atrophy in (medial) temporal lobe areas explains most of the variance in cognitive decline, especially memory dysfunction.

The concept of MCI is a heterogeneous clinical entity. On the one hand, it represents in many cases a prodromal state of Alzheimer’s disease (AD) (Defranceso et
Exploring the value of improved neuropsychological examination (Serra et al., 2013), but also patients who remain stable or show full or partial recovery after initial cognitive abnormalities (Diniz et al., 2009; Maioli et al., 2007; Mitchell & Shiri-Feshki, 2009; Visser et al., 2006). Part of this heterogeneity is due to a combination of genetic (Davatzikos, Bhatt, Shaw, Batmanghelich, & Trojanowski, 2011; Spampinato, Rumboldt, Hosker, & Mintzer, 2011) and behavioral factors (Serra et al., 2011). Another relevant source of variability in patients satisfying MCI criteria is the existence of various conditions other than neurodegeneration (Gauthier & Touchon, 2005). Indeed, we found that about seven percent of our patients showed evidence of non-credible performance, which corresponds to the rates that have been previously reported in medical or psychiatric cases not involving litigation or compensation (Mittenberg, Patton, Canyock, & Condit, 2002). However, this percentage was almost doubled in patients younger than 65 years of age. Also another study, investigating 286 consecutively referred patients in a metropolitan veterans affairs medical center, found that the patients showing non-credible performance were relatively young (mean age was 57 years; Axelrod & Schutte, 2010). In the Netherlands, for most people this is the retirement age. It is therefore tempting to hypothesize that SVT failure of these patients might be associated with psychosocial factors such as job dissatisfaction or wish for early retirement. Furthermore, our findings showed that, in patients exerting non-credible performance, there is virtually no correlation between hippocampal volumes and memory performance (Rienstra et al., 2013a) and that this group did not show cognitive decline after two years (Rienstra et al., 2013b). Moreover, we found evidence for significantly more emotional-behavioral complaints, especially symptoms of depression and anxiety (Rienstra et al., 2013a). It is also noteworthy that for one third of our patients with non-credible SVT results MRI data were not available because they declined cooperation due to claustrophobic complaints. Although many studies have shown that emotional problems like depression or anxiety disorders by themselves are not sufficient to cause SVT failure (Ashendorf, Constantinou, & McCaffrey, 2004; Rees, Tombaugh, & Boulay, 2001; Yanez, Fremouw, Tennant, Strunk, & Coker, 2006), it is conceivable that, compared to the general population, the risk of SVT failure is increased in individuals who present with emotional-behavioral problems or psychiatric disorders. It should be noted, however, that these findings could also be explained by overreporting of emotional symptoms in the SVT non-credible group. Non-credible cognitive performance and overreporting of emotional symptoms are correlated (Dandachi-Fitzgerald, Ponds, Peters, & Merckelbach,
In conclusion, the results of the studies presented in this thesis show that there is non-credible cognitive test performance in a subgroup of MCI patients, which, if undetected, will result in invalid MCI diagnoses.

The second main conclusion of this thesis is that brain atrophy in (medial) temporal lobe areas explains a large part of the variance in cognitive decline. Using a comprehensive battery of neuropsychological tests and a whole-brain VBM analysis approach, we found significant correlations between brain structure in about the same regions, mainly located in the temporal lobes, and neuropsychological tests tapping different cognitive functions. We found support for the assumption that these results are due to the primary neuropathology of memory dysfunction (Rienstra et al., under revision). By contrast, memory impairment itself appeared to be specifically related to lower volume of the left hippocampus. This pattern of results has also been found in a recent study evaluating associations between grey matter values and a measure of multiple cognitive domains capturing memory, language, visuospatial and executive abilities in a largely comparable mixed patient sample consisting of normal individuals, patients with MCI and subjects with dementia (Farias et al., 2013). In accordance with our results these authors found that only hippocampal volume was uniquely associated with the various cognitive domain scores. Therefore, based on our results and those of Farias et al. (2013) it can be concluded that relations between non-memory cognitive domains and brain atrophy in other structures than the temporal lobe are probably overshadowed by memory decline and temporal lobe atrophy, especially in early stages of the disease. Furthermore, it has been shown that left medial temporal lobe atrophy, or more precisely, atrophy located in the hippocampus and parahippocampal gyrus, is the most consistent neurostructural predictor to conversion to AD (Ferreira, Diniz, Forlenza, Busatto, & Zanetti, 2011).

7.4. METHODOLOGICAL CONSIDERATIONS
The major strength of the studies presented in this thesis lies in the nature of the patient sample: our cohort is likely to represent the kind of patients most dementia specialists deal with in their practices. We evaluated a large heterogeneous, naturalistic sample of elderly patients referred to memory clinics. For all participants the differential diagnosis included a possible early stage of dementia at the time of referral. Unlike most previous studies on cerebral correlates of neuropsychological deficits, we did not limit our sample to strictly selected patients fulfilling MCI criteria highly predictive for the development of dementia and without psychiatric co-morbidity. Instead, we
only excluded clear dementia cases, so that we retained a more representative mix of ‘difficult’ memory clinic patients. This aspect will enhance the generalizability of our findings to clinical practice in memory clinics. Second, the extensive neuropsychological evaluation tapping multiple cognitive domains in combination with high-resolution magnetic resonance imaging (MRI), and a whole-brain VBM analysis approach in our large sample made it possible to test the domain specificity of volumetric associations with neuropsychological test performance. Similar studies usually examine just a single cognitive domain. Third, our study is longitudinal, which is an important methodological strength when the subject is cognitive decline or dementia.

Some methodological limitations of the current research should also be addressed. The first concerns the small size of the non-credible SVT group. Using a report on a large sample of consecutive patients referred to a university based memory clinic (Hejl, Hogh, & Waldemar, 2002) as a guideline, we expected to find about 35% uncertain pre-dementia diagnoses mostly due to emotional or behavioral problems, before starting our project. However, the percentage appeared to be considerably lower. One explanation for this low incidence may be the type of referrals to our project. We recruited the major part of our sample in neurological memory clinics. Although depression is a common diagnosis in this type of clinic (Hejl et al., 2002), one might expect a higher proportion of SVT failure in patients from psychiatric memory clinics. Furthermore, it is quite possible that the low incidence of non-credible performance in our study might be caused by a selection bias. Exaggeration of symptoms or impairments is probably a common cause of non-credible performance in clinical practice when patients feel the need to get recognition for their complaints (Miller, 2001). Our patients were asked to take part in a research project, which inherently implies recognition for their complaints. This may have reduced any tendency to exert non-credible performance. This assumption is supported by the observation that some patients who were referred to our study, had non-credible test results on a previous neuropsychological examination, but actually performed above the cut-offs for non-credible performance when tested in the context of our research project.

A second methodological issue is that, due to a shortage of financial means, we were unable to collect MRI data of a healthy control group. This prevented us to compare the grey matter tissue between credibly performing patients, non-credible patients and healthy controls. It would have been interesting to examine brain-behavior relationships in healthy individuals and to compare them with those found in the other study groups. This information probably could have provided more information about the dominance of temporal lobe atrophy and memory impairment in genuine MCI patients.
Third, besides brain atrophy, we did not include other biomarkers of AD. Among several potential diagnostic biomarkers, the most consistent findings have been obtained with the measurement of cerebrospinal fluid (CSF) concentrations of β-amyloid peptide 42 (Aβ42) and levels of total tau (T-tau) and phosphorylated tau (P-tau). AD patients characteristically display low concentrations of Aβ42 and high concentrations of T-tau and P-tau. This pattern of CSF biomarkers is commonly referred to as the ‘AD signature’ (Forlenza, Diniz, & Gattaz, 2010). MCI patients who convert to AD within a few years have a CSF biomarker pattern indistinguishable from the pattern found in patients with dementia of the AD type. MCI patients with progressive deficits (albeit not severe enough to characterize conversion) also have a pattern similar to AD patients. Conversely, patients with unstable (transient MCI) or non-progressive cognitive deficits (stable MCI) typically have a CSF biomarker pattern very similar to that found in healthy older adults (Forlenza et al. 2010). It would support the findings of our study if it could be shown that the CSF biomarker pattern of non-credible patients is similar to that of healthy control subjects.

Fourth, one might object that by examining a relatively unselected sample of memory clinic patients we neglected the etiology of the impairments. Admittedly, brain–behavior relations may be different across diseases. Yet, we do not think this objection is valid since we excluded other neurological causes than neurodegenerative brain disease. With a few exceptions, the large majority of patients who declined over the next two years satisfied either MCI or AD criteria at follow-up (Schmand et al., 2014). Thus, the baseline sample on which we report in this thesis mainly consisted of three main categories: worried well, patients who had a psychiatric disorder but were not in a dementia trajectory, and patients who had MCI or dementia due to a neurodegenerative disease. Since for some of the studies we also excluded patients with non-credible test performance, we assume that the subgroup of patients with a psychiatric disorder but no neurodegeneration showed the usual brain–behavior relations of healthy elderly.

Finally, there was a considerable loss to follow-up (35% of the patients), which may have biased our results. Taking the group classification of chapter 6 as a starting point (i.e. non-credible performance, dementia profile, normal effort scores), there was a significant difference in attrition rates between groups (p = 0.05). Most patients were lost to follow-up in the older group with the dementia profile (46%), followed by the group of participants with non-credible performance (34%) and the group with normal effort scores (27%). This is likely to have affected the findings of this study, because the most severely impaired patients at baseline could be expected to exhibit...
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a faster rate of cognitive decline. Thus, our longitudinal data are likely to have given a conservative estimate of cognitive change.

7.5. RELEVANCE AND IMPLICATIONS FOR CLINICAL PRACTICE

The findings in this thesis have several important clinical implications. The clinical implications of our preparatory studies on the employability of SVTs are that our improved reference data for the WMT increase the efficiency of a neuropsychological evaluation and will lead to improved interpretation of the WMT profile of subtest scores. The results of the second part of our research have shown that brain-behavior relations may be obscured and the diagnosis of a preclinical dementia stage may be invalid in patients who do not perform to the best of their ability during cognitive evaluation. This underscores the importance of administering formal tests of symptom validity in the examination of patients who present with cognitive complaints that may signify an early stage of dementia, especially when patients are below 65 years of age. If neuropsychologists administer SVTs in their diagnostic routine, it will help to improve the predictive validity of the MCI concept by averting false-positive diagnoses of (early) dementia (Heilbrunner, Sweet, Morgan, Larrabee, & Millis, 2009). By administering SVTs in the examination of these patients, clinicians will be able to divide the population of suspected pre-dementia patients into three subgroups. The first group will be composed of patients with normal SVTs and abnormal cognitive tests. These will be the patients with validly and reliably established cognitive disorders. If diagnostic work-up excludes other etiologies than degenerative brain disease, these patients are likely to convert to dementia in the years to come. The type of cognitive impairment and other clinical characteristics will determine to what type of dementia a patient will convert (Dubois et al., 2007; Serra et al., 2013). The second group will contain patients with abnormal SVTs and abnormal cognitive tests. Strictly speaking it is uncertain whether or not these patients are in a pre-dementia stage, because the presence of cognitive impairment has not been validly established nor has it been disproven. However, in these patients an emotional-behavioral or psychiatric etiology is much more likely, whereas a degenerative dementia is much less likely than in the first subgroup of patients. Psychiatric evaluation is important in this second category in order to establish alternative diagnoses and to install adequate treatment or other patient care. The third group will consist of patients with normal SVTs and normal cognitive tests. These patients, although complaining of mental dysfunction, do not show objective evidence of cognitive impairment. Some may just be overly concerned about their mental state but otherwise physically and mentally healthy. Others may
suffer of emotional, behavioral or psychiatric problems similar to those of the second subgroup, with the only difference that they invested normal effort during cognitive testing. Psychiatric screening is also important in this category.

Furthermore, the results of part II underscore the importance of administering all WMT subtasks to fully understand the profile. The results on the first three easy subtests must be placed in the context of the last three conventional tests of verbal memory. In this way, the WMT dementia profile not only aids in interpretation of the WMT results when it is utilized as a SVT, but also provides clinically relevant information on (future) cognitive impairment and early dementia.

7.6. RELEVANCE AND IMPLICATIONS FOR SCIENTIFIC RESEARCH
The results from our studies demonstrated that undetected, non-credible cognitive test performance in a subgroup of patients will result in invalid MCI diagnoses. From a researcher’s point of view, these patients are a methodological nuisance, causing noise in the data. The possibility that a negative response bias may be a contaminator of scientific data has been discussed before, in particular in the context of post traumatic stress disorder and sexual abuse by Catholic Church officials (Freeman, Powell, & Kimbrell, 2008; Geraets et al., 2009; Merckelbach, Langeland, de Vries, & Draijer, 2014; Rosen, 2004; Rubenzer, 2009). The conclusion that arises from this discussion is that in some scientific contexts possible response bias should be checked for, and invalid responders should be cleaned from the study samples. Otherwise, research data may not only be contaminated, but yield wrong conclusions, which do not correspond to the real facts. In this study the percentage of patients who failed SVTs was not excessively high. Undetected noise would not have affected our data very much. In settings where this percentage is higher, however, it could significantly obscure brain-behavior relations. We assume that this is particularly problematic in many psychiatric contexts (see e.g. Gorissen, Sanz, & Schmand, 2005; Stevens, Fabra, & Thies, 2014; Van Egmond, Kummeling, & aan Bal kom, 2005). If researchers of the early stages of dementia apply SVTs, they may avoid this type of ‘pollution’ of their samples, thus increasing the statistical power of their studies, and decreasing the budgets necessary to conduct the research.

7.7. RECOMMENDATIONS FOR FUTURE RESEARCH
In view of the growing prevalence of dementia worldwide, there is an urgent need for the development of better diagnostic tools and more effective therapeutic interventions. At the earliest stages of AD, until now no conventional clinical methods can guarantee perfect predictive validity. New technologies based on structural and
Exploring the value of improved neuropsychological examination functional neuroimaging (such as amyloid imaging; Petrella, 2013), and on the biochemical analysis of CSF may reveal correlates of intracerebral pathology in individuals in the pre-clinical stages of the disease. However, since the clinical symptoms of dementia are of a behavioral nature, accurate early assessment of symptoms based on behavioral methods will probably always be of vital importance.

The overall objective of this thesis was 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 pre-clinical stage of the disease by applying SVTs to detect non-credible performance. Contrary to our expectations, the incidence of non-credible performance in our cohort was considerably low. This does not imply, however, that the influence of non-credible performance on neuropsychological test results may be ignored. Therefore, the first recommendation is to study more extensively the influence of non-credible performance on neuropsychological test results in patients suffering from a possible early stage of dementia by expanding the type of referrals. Based on our results, we expect to find a higher proportion of SVT failure in patients from psychiatric memory clinics, especially when they are younger than 65 years of age.

Second, besides non-credible performance, there is another cause for the lack of predictive validity of behavioral methods for the early diagnosis of dementia. That is, the relatively low reliability (reproducibility) of neuropsychological tests, in particular memory tests, used to establish cognitive abnormality (Lezak, Howieson, Bigler, & Tranel, 2012). The validity of a diagnosis is limited by the reliability of the diagnostic instruments used. Therefore, the detection of pre-dementia stages can also be improved by applying existing behavioral methods in such a way that they measure cognitive functions more reliably than some of the tests now frequently used in clinical practice. One way to raise the test reliabilities is to use the classical method of test elongation, i.e. applying more trials of the same task. Actually, we already developed new versions of existing neuropsychological tests with proven validity and administered them at baseline. However, before we will be able to test if more reliable cognitive tests indeed improve the prediction of conversion to dementia, these assessment tools need to be investigated in future research to establish appropriate cut-off points and reliable reference data.
References


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