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Assessment of
everyday memory
in patients
with alcohol-related
cognitive disorders
using the
Rivermead Behavioural
Memory Test

Arie Wester

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Assessment of everyday memory in patients
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using the Rivermead Behavioural Memory Test

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CHAPTER

General Introduction





Introduction

Alcohol use accounts for the majority of the treatment demand in addiction care. The primary problem in 47% of over 70,000 individuals seeking treatment in the Netherlands in 2012 was alcohol-related. In alcohol addiction care, about 20% of clients (over 7,000 in 2012) are first-time care seekers. This implies that almost 80% of those seeking treatment for their alcohol addiction have done so before. In about 25% of the cases the alcohol problems coincide with the abuse of other substances or with gambling, which is lower compared to the rates recorded for other primary substances. The greater majority of the alcohol-related care seekers thus do not use or abuse other substances (Wisselink, Kuijpers, & Mol, 2013).

A large proportion of individuals with alcohol dependence show cognitive impairment, ranging from subjective complaints that cannot be detected using cognitive testing, to mild and very severe disorders as seen in, for instance, Korsakoff's syndrome. These cognitive impairments encompass deficits in memory, executive functioning, visuospatial capacities, psychomotor abilities and emotional functioning. There is growing evidence that cognitive impairment contributes to poor treatment outcome, stressing the importance of identifying cognitive dysfunction by means of neuropsychological assessment.

Plenty of research on cognitive functioning, especially of memory functioning, has been done in the field of Korsakoff's syndrome. Relatively few studies have been published investigating memory impairments in alcohol-dependent individuals without Korsakoff's syndrome. Much of the research centres around explanations for the difference between Korsakoff's syndrome and long-term alcohol abuse, for instance focusing on the temporal gradient in (retrograde) memory (Kopelman, 1989) or the continuity hypothesis that states that the neuropsychological performance of alcoholics depends upon the amount and number of years of alcohol consumption (Butters & Brandt, 1985; Ryback, 1971). Less attention has been paid to cognitive impairment in non-Korsakoff chronic alcoholics. From a clinical perspective, it is the heterogeneity and the graded nature of alcohol-related impairments that make it difficult to discriminate on the one hand between alcoholics with and without memory disorders, and Korsakoff's syndrome or alcohol-related dementia on the other hand. To our knowledge, no systematic study has been done on the sensitivity and specificity of neuropsychological memory tests to differentiate between these patient groups.

Traditionally, 'classic' memory test are mainly used in the assessment of neuropsychological patients. However, these tests appear to be weakly correlated with subjective memory complaints and problems in everyday memory function

(Reid & MacLulich, 2006). In the last two decades a gradual shift has occurred in the use of neuropsychological tests away from diagnostic questions about the presence or localization of brain pathology, or merely determining and describing impairments, to treatment-oriented questions that lay a bridge between diagnosis and rehabilitation (Chaytor & Schmitter-Edgecombe, 2003). To answer these questions, neuropsychologists have focused on the assessment of cognitive abilities of patients that are needed in everyday life to a greater extent. However, traditional tests that have been developed to assess diagnostic questions may not be suited to answer these questions. This problem refers to the concept of 'ecological validity' in neuropsychology. Higginson et al. (2000, p 185) define ecological validity, in neuropsychological settings, as the "... functional and predictive relationship between the client's performance on a set of neuropsychological tests and the client's behaviour in a variety of real-world settings (e.g., at home, work, school, community, etc.)". Ecologically valid tests can be seen as complementary to traditional tests. These tests aim to determine whether or not a patient has difficulties in real-life, and the traditional tests inform us of what kind of memory system is affected.

Construct of ecological validity

Two approaches have been identified in creating ecological validity in neuropsychological tests: verisimilitude and veridicality (Chaytor & Schmitter-Edgecombe, 2003). Verisimilitude refers to the similarity between the cognitive demands of a test and the cognitive demands in the everyday environment. Verisimilitude requires that a test attempts to simulate critical everyday cognitive tasks, in order to capture the essence of an individual's ability to perform those tasks in reality. Hence, these tests primarily try to identify people with limited functional abilities rather than trying to detect brain injury or determining the extent of brain damage (Chaytor & Schmitter-Edgecombe, 2003). With this theoretical concept in mind several standardized instruments were developed, including the Rivermead Behavioural Memory Test (RBMT; Wilson et al., 1985) for the assessment of everyday memory problems or the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996) for measuring aspects of executive function. Verisimilitude is more related to the concept of 'face validity', which is a very basic form of validity which determines whether a test appears to test what it, on the surface, is supposed to test. While verisimilitude may not per se enhance a test's diagnostic accuracy, its close relation with everyday function may increase a patient's motivation to participate and cooperate in neuropsychological assessment.

Veridicality refers to the degree to which results obtained with existing instruments are related to other measures that predict everyday functioning. To determine veridicality, statistical methods are used to investigate the relationship between the performance on traditional neuropsychological tests and measures of everyday functioning. The notion of veridicality is akin to 'predictive validity', which refers to the agreement between scores or results on a diagnostic test and performance on other – typically more functional or everyday-life – measures (e.g., does performance on a word-recall test predict the degree of independent functioning in daily life). Traditional test may be predictive of everyday cognitive functioning, even when they have not been devised to mimic everyday life activities (Kibby, Schmitter-Edgecombe & Long, 1998). The challenge with veridicality is to determine the optimal outcome measure that should be predicted by test performance. Because both approaches have their strengths and limitations, a combination of the two approaches is often taken to create an ecologically valid instrument (Chaytor & Schmitter-Edgecombe, 2003).

Ecologically valid memory assessment

In 1985, Barbara Wilson and colleagues developed and published the RBMT. The authors' intention was to provide a test that was able to determine and predict memory problems in daily living in people with brain injury. Furthermore, the test should be able for monitoring changes over time in order to evaluate the effects of interventions or spontaneous recovery, for instance in a rehabilitation setting. The RBMT consists of tasks analogous to everyday circumstances that appear to be a problem for people with brain injury. The subtests relate to remembering to execute an everyday task or to the retention of information necessary for everyday functioning, such as faces, stories or routes. Various research studies have shown that the test has good ecological validity. In 1987, Van Balen & Groot Zwaaftink published an translated and adapted version in the Dutch language. This Dutch version of the RBMT appeared to be a useful instrument for assessing everyday memory problems (Van der Feen, Van Balen & Eling, 1990). Stratified norms for the RBMT have also been published (Van Balen & Wimmers, 1992; Van Balen, Westzaan & Mulder, 1996).

Because the original RBMT was not found to be sensitive enough to detect mild memory deficits, the Rivermead Behavioural Memory Test – Extended Version (RBMT-E) was developed (Wilson et al., 1999). In order to make the RBMT-E more difficult than the RBMT, the original four parallel versions were combined into two parallel versions, resulting in a higher number of items for

most subtests. In 2003, the Second Edition of the Rivermead Behavioural Memory Test (RBMT-II) was published (Wilson et al., 2003) that basically updated some of the items or materials. Finally, in 2008, a completely revised test battery was launched, the Rivermead Behavioural Memory Test-Third Edition (RBMT-3). This version contains a number of subtests that have been retained from the RBMT-II along with one new subtest – the Novel Task (Wilson et al., 2008).

Aim and outline of this thesis

The objective of the present thesis is twofold. First, the applicability of the RBMT in alcohol-related cognitive disorders will be studied. Next, the development of the Dutch version of the RBMT-3 is presented and its psychometric properties as well as its applicability in patients with alcohol-use disorder will be examined.

The thesis starts in **Chapter 2** with an overview of the type of cognitive disorders that can be the consequence of alcohol abuse or alcohol dependency. In **Chapter 3** an analysis of the performance on the RBMT of 322 patients with Korsakoff's syndrome is presented. **Chapter 4** directly compares the RBMT with the Dutch version of the California Verbal Learning Test (CVLT) in Korsakoff patients versus alcoholics with and without cognitive impairments. **Chapter 5** describes a study on the reliability and validity of the Rivermead Behavioural Memory Test-3 in healthy participants. Next, a study is presented that examines whether the RBMT-3 is an improvement over the original RBMT with respect to diagnostic accuracy and reducing the problem of ceiling and floor performances (**Chapter 6**). **Chapter 7** describes the sensitivity and specificity of the RBMT-3 as studied in Korsakoff patients, patients with alcohol dependency and healthy controls. **Chapter 8** looks into the discriminatory power of a short cognitive screening, the Montreal Cognitive Assessment (MoCA), in relation to performance on the RBMT-3 in diagnosing patients with alcohol-related cognitive impairments and predictive capacities with regard to the severity of memory impairment. Finally, **Chapter 9** summarizes and discusses the main results of the reported studies, and addresses the clinical implications of the findings.

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CHAPTER

Alcohol-related cognitive disorders: a review

Based on:

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Boom, Amsterdam.



Abstract

In addiction care, most individuals seeking help do have problems in alcohol use. However, prolonged alcohol use, may cause damage to the brain, potentially producing cognitive deficits that may range from mild to a alcohol-related dementia (ARD). These impairments probably, may be attributed to the direct neurotoxicity of alcohol. Brain structures that appear to be most vulnerable to the effects of alcohol are the neocortex, the limbic system, hippocampus and cerebellum. In combination with malnutrition, resulting in thiamine deficiency, Korsakoff syndrome may be the result as well. Neuropathological changes concern petechial haemorrhaging, specifically in the corpora mammillaria, the thalamus, and various structures around the third and fourth ventricles. Korsakoff syndrome is characterized by severe amnesia, especially anterograde amnesia, and executive dysfunction. In clinical practice, delineating cognitive deficits resulting from alcohol use, the Korsakoff syndrome or alcohol-related dementia may be difficult, as for all these conditions clear biomarkers are to date lacking. Moreover, the abnormalities in the brain supposed to underlie Korsakoff syndrome cannot be easily detected by conventional brain imaging techniques. Lastly, alcohol-related dementia is a syndromal diagnosis without a discrete neuroanatomical substrate. Also, consensus on the clinical criteria of the Korsakoff syndrome and ARD, the criteria of which never have been fully accepted, is changing. Nevertheless, a thorough analysis of the cognitive and psychological functioning of individual patients with alcohol-use disorders, is always recommended.

Epidemiology

Alcohol use accounts for the bulk of the treatment demand in addiction care. The primary problem in 47% of the well over 70,000 individuals seeking treatment in the Netherlands in 2012 was alcohol-related. Of these help-seekers about 30% are women, a percentage that has remained stable for many years. The average age of alcohol-related care-seekers is 46 years. However, the percentage of treatment-seekers over the age of 55 has been showing a marked increase of late. The overall share of young adults has increased slightly, with 5% of the young clients being under the age of 25. In alcohol rehabilitation, about 20% of clients (over 8,000 in 2010) are first-time care-seekers. This implies that almost 80% of those seeking treatment for their alcohol addiction have done so before. In 24% of cases the alcohol problems coincide with the abuse of other substances or with gambling, which is relatively low compared to the rates recorded for other primary substances. The greater majority of the alcohol-related care-seekers do not use or abuse other substances. Over 8% of the treatment population also takes hard drugs (opiates, cocaine and amphetamines), which use is categorised as a secondary problem (Wisselink, Kuijpers, & Mol, 2013).

Prolonged and excessive use of alcohol (for the definitions of alcohol use, misuse and abuse, see Table 1) may result in cognitive impairment. Although proportions reported in the literature vary, it is estimated that about half of those seeking treatment for their alcohol dependency suffer from a cognitive disorder. The deficits may manifest themselves well before any alcohol-related neurological symptoms become evident and may have serious implications for eventual treatment success and everyday functioning.

Table 1 Classification of alcohol use

	Men	Women
Moderate drinking	≤ 21 units/week	≤ 14 units/week
Heavy drinking	22-50 units/week	15-35 units/week
Excessive drinking	>50 units/week	>35 units/week
Episodic excessive drinking	2 or more days/week 6 units or more	2 or more days/week 5 units or more

A unit is defined as a standard glass of appr. 10g of pure alcohol (Nederlandse Vereniging voor Psychiatrie, 2009)

About 10% of alcohol abusers exhibit severe cognitive impairments, one of which is alcoholic Korsakoff's syndrome (Rourke & Grant, 2009). The causes underlying both the short- and the long-term consequences of alcohol abuse are only partially understood and are assumed to be multifactorial (Nederlandse Vereniging voor Psychiatrie, 2009).

Alcohol can affect the nervous system in various ways. First, there is some evidence to suggest that it has a direct neurotoxic effect on neurons and axons. Second, indirect neurotoxic effects of high calcium concentrations in the neurons have been found after sudden alcohol withdrawal. A third mechanism is the irreversible disruption of physiological processes through chronic vitamin deficiency (i.e. a lack of thiamine or vitamin B1). As these three mechanisms co-occur in most chronic alcohol abusers, it is difficult to determine the distinct contributions of each mechanism. Also, some chronic alcoholics may have sustained damage due to other causes indirectly related to their alcohol use, such as hepatic encephalopathy or traumatic brain injury.

Changes in cognitive functioning already occur in the period immediately after the intake of alcohol. Thus, reaction speed is reduced after ingestion of as little as 1-2 units (Schweizer & Vogel-Sprott, 2008). Excessive consumption of alcohol also induces changes in other cognitive domains. These acute effects concern explicit memory impairment (particularly during and after an episode of heavy drinking) as well as prospective memory deficits. In addition, performance decrements are seen in the perception of emotions, while errors increase when rating the intensity of facial expressions (Fernández-Serrano, Pérez-García & Verdejo-García, 2010). Moreover, excessive consumption of alcohol results in loss of response inhibition and behavioural control. In this chapter we will, however, focus on the chronic effects of prolonged alcohol use.

The neurotoxicity of alcohol

In his overview of the effects alcohol exerts on the brain, Arts (2005) describes how alcohol dampens the brain's functioning by stimulating the GABA system, which inhibits neurotransmission throughout the brain, disrupting motor control and coordination, and cognitive functioning. Through an inhibition of the NMDA receptor channel complex, which is part of the excitatory glutamate system, cognitive impairments develop, most notably memory deficits. As the glutamate system counteracts the effects of the alcohol-induced inhibition by upregulating NMDA receptors, their numbers as well as their sensitivity increases. When the consumption of alcohol is ceased, this may lead to an overstimulation of the neurons, resulting in withdrawal symptoms but also irreversible damage to

brain cells. This accordingly implies that peaks in alcohol consumption, as in binge drinking, have more severe effects than regular consumption.

There are indications that the harmful effects of alcohol are not similarly detrimental across the lifespan. Both animal and human studies have shown that particularly during adolescence the developing brain is highly susceptible to its adverse effects. In this context, Boelema, Ter Bogt, Van den Eijnden, and Verdurmen (2009) pointed to animal studies demonstrating that young animals are less affected by the sedative effects of alcohol, with their motor control and coordination being less impaired than is seen in adult animals. Adolescents would thus be able to consume more alcohol than adults before experiencing any acute problems, but with an increased risk of sustaining brain damage. It is known that children and young adults with an alcohol dependency show deficits in language, attention, learning, (prospective) memory, spatial ability, and the detection of subtle changes in facial symmetry. Yet, these findings are not very robust as the studies do not disclose any details about premorbid cognitive functioning: Did the youths suffer brain damage as a result of their alcohol use or did they start abusing alcohol because of abnormal brain functions (e.g., an innate increased impulsivity or propensity to risk-taking behaviour) and hence pre-existing diminished cognitive capacities? Most studies, moreover, concerned adolescents whose alcohol use was categorised as extreme. It is hence arguable whether the findings from these studies can be generalised to Dutch adolescents that drink heavily but are not alcohol dependent (see also Table 1).

Neuroimaging and neuropathology

Imaging and neuropathological research has learned that the following brain structures are most vulnerable to the effects of alcohol: the neocortex (specifically the frontal lobes), the limbic system (i.e., the hypothalamus), the hippocampus and the cerebellum. Numerous studies suggest that the frontal brain regions are more susceptible to alcohol-related damage than other areas. In his post-mortem studies Harper (1998) found a selective loss of cortical neurons in the frontal cortex. Brain imaging studies (MRI) also show volume loss in the frontal lobes. Even before significant frontal brain shrinkage and cognitive problems become manifest, frontal perfusion and metabolism were demonstrated to be reduced in abstinent alcohol addicts compared to the values found for matched, non-alcoholic controls (Volkow et al., 1992). Cerebellar atrophy, most notably the white matter of the cerebellar vermis, is seen in many (25-40%) alcoholics. With concomitant thiamine deficiency the number even increases to 35-50% (Victor, Davies, & Collins, 1989). As to the hippocampus, structural imaging studies have shown

volume loss in alcoholics, which is attributed to the changes in hippocampal white matter. With total abstinence (i.e. complete cessation of alcohol use) this loss appears partially reversible, as is the case with the cognitive deficits. Alcohol-related damage to the corpora mammillaria, part of the hypothalamic diencephalon, is taken to underlie alcoholic Korsakoff's syndrome (Oscar-Berman & Evert, 1997), in addition to lesions of the hippocampus, fornix, and medial and anterior thalamic nuclei (Visser et al., 1999).

Cognitive disorders

Much of the research into the neuropsychological effects of alcohol use was conducted in populations of medically hospitalised alcohol-dependent patients. Following a brief period of abstinence (< 30 days) patients displayed significant symptoms in the impulsivity domain, among other aspects in response inhibition and risk taking (Bjork, Hommer, Grant, & Danube, 2004). In their review, Fernández-Serrano and colleagues (2010) report that comparable patient samples showed a decline in their abstracting and problem-solving abilities, as well as diminished cognitive flexibility, attention and perceptuomotor speed. With regard to memory functions, it took patients more time to learn new information and they had more difficulty reproducing what had been learned (free recall). In a sample of alcoholics who had remained abstinent for 32 days, changes were observed in verbal episodic memory only (Errico, King, Lovallo, & Parsons, 2002). Fein, Torres, Price, and Di Sclafani (2006) demonstrated that in most patients the cognitive deficits associated with their alcohol abuse had disappeared after prolonged abstinence (> 6 years). Some will nevertheless continue to experience problems in visuospatial abilities, decision-making and executive functions.

Because the behaviour of alcoholics - e.g. a loss of control, the inability to abstain from alcohol, habitual behaviour and a lack of planning - in many aspects resembles that seen in patients with lesions in the orbitofrontal cortex, Ihara, Berrios, and London (2000) investigated whether the former also suffer from the dysexecutive syndrome. Based on their research, they distinguished four patterns of cognitive dysfunction in alcoholics: (1) impaired executive functions with intact intelligence and memory, (2) concomitant executive and memory deficits with undisturbed intelligence, (3) overall cognitive decline, and (4) intact cognitive abilities. About two-thirds of their patients fell within the first two categories. This suggests that in the treatment of individuals with chronic alcoholism a detailed neurological examination is pertinent in order to gain insight into the underlying mechanisms.

The executive impairments in alcoholism mainly pertain to cognitive flexibility, problem solving, verbal and nonverbal abstraction, and decision making. So-called gambling tasks in particular uncovered that alcoholics are predominantly guided by short-term gains, irrespective of the longer-term consequences. Compared to controls, long-term abstinent alcoholics more frequently take decisions that tend to backfire (Feinn, Klein, & Finn, 2004). The extent to which they made disadvantageous decisions was also found to be associated with the duration and extent of their alcohol use. Despite their decision-making deficits, the alcoholics did succeed in maintaining prolonged abstinence. Fein and colleagues suggest that in those who are unable to do so the decision-making capacity is more severely impaired. In addition to impaired decision making, they found their alcoholic group to show more socially deviant behaviour and an inadequate coping style, with a tendency to externalise problems.

Studies of social cognition in alcohol dependents focus on their ability to resolve interpersonal problems and to interpret affective prosody and facial expressions (Uekermann & Daum, 2009). Even though alcoholics are aware of what is expected of them in interpersonal problem-solving situations, they persist in their habitual, inadequate and inappropriate response behaviours, which may result from a diminished inhibition capacity. The ability to perceive emotions is another prerequisite to correctly interpret the intentions of others. Various studies show that alcoholics are less accurate than control populations in recognising emotional facial expressions and prosody. They make more errors when asked to recognise facial expressions in general, while they tend to label sad expressions as hostile towards them (Frigerio, Burt, Montagne, Murray, & Perrett, 2002). As yet little is known about their social cognition in more complex conditions such as understanding humour, although there are indications that alcoholics have difficulty capturing the humour in (complex) jokes. According to Uekermann and Daum (2009) these problems are partly caused by the incremental role of the executive component in second and third-order 'Theory-of-Mind'.

An important question is whether in alcohol-related cognitive dysfunction a dose-response relationship plays a role. In other words, do the duration and magnitude of lifetime alcohol consumption unequivocally correlate to the severity of the cognitive impairment? The so-called continuity hypothesis takes its lead from this association: it assumes a continuum of damage, with social drinkers at one extreme, alcohol dependents in the middle, and alcoholics with severe cognitive decline, as seen in Korsakoff's syndrome, at the other extreme, with the latter decline resulting from a combination of prolonged, excessive drinking and vitamin deficiency (see Butters and Brandt, 1985). The hypothesis

is, however, only partially supported by empirical evidence. While on the one hand there is clear evidence to suggest that long-term alcohol abuse causes more severe cognitive impairment (Parsons & Nixon, 1998), the brain damage incurred by long-term alcoholics is, on the other hand, not necessarily identical to the abnormalities seen in the brains of Korsakoff patients. Thus, the latter population has been found to display deficits in all aspects of executive functioning, whereas in non-Korsakoff chronic alcoholics the executive deficit is more specific. This is demonstrated by the object-alternation paradigm, i.e. tasks requiring continuous response adjustment. The duration of alcohol abuse proved to be strongly correlated with performance on this paradigm (Brokate et al., 2003). Accordingly, today the cumulative cerebral effects of long-term alcohol abuse are as such distinguished from pathology secondary to the abuse. For example, prolonged malnutrition is taken to underlie Korsakoff's syndrome, while cerebrovascular damage resulting from the unhealthy lifestyle of alcohol addicts may also cause cognitive impairment.

Korsakoff's syndrome

Korsakoff's syndrome is named after the Russian psychiatrist Sergei Korsakoff who in 1887 provided an in-depth description of the disorder. In the DSM-IV-TR the syndrome is defined as an alcohol-induced, persisting amnesic disorder, manifested by impairment in the ability to learn new information or the inability to recall previously learned information, causing significant impairment in social or occupational functioning and a significant decline in the level of previous functioning. The memory disturbance does not exclusively occur during the course of a delirium or a dementia and persists beyond the usual duration of alcohol intoxication or withdrawal. Additionally, there must be evidence from the history, physical examination or laboratory findings that the memory disturbance is not caused by any direct physiological impairments resulting from somatic disorders (including physical trauma). There are no recent or reliable prevalence data of Korsakoff's syndrome in the Netherlands. The only available figures are given by Blansjaar, Horjus, and Nijhuis (1987) and pertain to the district of The Hague. Based on extrapolations from these figures and other data, the prevalence rate of Korsakoff's in the Netherlands is estimated to be between 5,000 and 15,000.

The fallacy that Korsakoff's syndrome is *caused* by long-term alcohol abuse is widespread. It was Sergei Korsakoff who already observed that, although the correlation with alcohol abuse was high, many of his patients had no drinking problems but did suffer from a whole host of gastrointestinal complaints. It was

not until much later that it became apparent that Korsakoff's syndrome was an indirect effect of alcohol abuse and should be seen as a residual impairment due to prolonged thiamine (vitamin B1) deficiency associated with the alcohol addiction. There are indications that 30 to 80% of individuals with an alcohol addiction have some degree of thiamine deficiency, where a severe deficiency may cause Wernicke's encephalopathy, an acute neuropathological syndrome typically characterised by ataxia, nystagmus, ophthalmoplegia, confusion and apathy. Because not all symptoms are always manifested - sometimes patients may present with only one or two - Wernicke's encephalopathy may be difficult to diagnose (Kessels, 2010). A study by Harper, Giles, and Finlay-Jones (1986) showed that as little as 16% of the patients in whom post-mortem abnormalities from a past Wernicke episode were found had been diagnosed with Wernicke's encephalopathy during their lifetime.

The neuropathological abnormalities concern petechial haemorrhaging, specifically in the corpora mammillaria, the thalamus (i.e. the mediodorsal nucleus) and various structures around the third and fourth ventricles. Although, in principle, Wernicke's encephalopathy is reversible if treated early by administration of vitamin B1, 80 to 90% of alcoholic patients diagnosed with the condition go on to develop Korsakoff's (Bodani, Reed, & Kopelman, 2009), which is why the disorder is also denoted as the Wernicke-Korsakoff syndrome.

As related above, the histories of the greater majority of Korsakoff patients make no mention of Wernicke's encephalopathy. This is explained by the fact that the syndrome can develop slowly at a subclinical level, while the diagnosis may also be missed due to an atypical course.

The cognitive deficits in Korsakoff's syndrome are associated with an almost complete lack of awareness and insight into the illness. Another typical feature of Korsakoff's is spontaneous confabulation, which in this syndrome implies that patients are prone to spontaneously tell untruths, for instance about their past or about their activities of the day, and also act upon these fabrications.

The memory deficit mainly concerns a very severe impairment of anterograde memory, which entails impaired imprinting as well as reduced memory recall, often coinciding with impaired memory search strategies. The literature typically states that working memory is intact. Robust neuropsychological assessment in clinical practice, however, shows that also working memory tends to be affected, which is not surprising given it is (partly) overlapping with executive functioning. Retrograde memory functions may also be disrupted in a temporal gradient, where knowledge of events from more recent years is most affected, while knowledge from events in the more distant past remains relatively intact. Nevertheless, in recent autobiographical memory 'isles of

memory' may persist, with the onset of retrograde amnesia often remaining unclear. Besides having problems remembering facts and events, Korsakoff patients also have difficulties placing memories in time. This inability may induce them to tell stories that, apparently, do not make any sense. On closer inspection, these accounts often appear to be composed of shards of memories that are themselves accurate but whose events have never transpired in the context painted by the patient. Thus, and contrary to what has been claimed, confabulations in Korsakoff's syndrome do not result from the gaps in the patients' memory that they try to mask by telling 'fibs'; we now know that confabulating tendencies have a different origin, given that they are also seen in patients without amnesia (and may even be elicited in healthy individuals). Possible cognitive accounts for confabulation behaviour are (1) reduced executive control, causing incorrect memories to be recalled (impaired strategic retrieval); (2) temporal confusion, causing accurate memories to be misplaced in time; and (3) impairments in reality monitoring, causing a discrepancy between current reality and retrieved memories. Rather than being suppressed or distorted, fragmented recollections from the past are erroneously activated as if they were, and subsequently linked to present reality. Although it is often presented as being typical to Korsakoff's syndrome, spontaneous confabulating is most prominent in the acute stages (following Wernicke's encephalopathy). Outside the acute phase these spontaneous confabulating tendencies will gradually fade or sometimes even fully disappear. In test conditions it is, however, possible to still evoke confabulations in patients in the chronic stages of Korsakoff's (Kopelman, 1987).

Another salient manifestation of the memory impairment is the disorientation in time, place and person. It is striking that, in contrast to the deficits in explicit memory, implicit memory functions remain relatively unaffected. Thus, motor learning is intact in Korsakoff patients (Van Tilborg, Kessels, Kruijt, Wester & Hulstijn, 2011), allowing them to 'automatically' master all kinds of skills, for instance memorising a route to be walked (Kessels, Van Loon & Wester, 2007).

Although the definition of Korsakoff's syndrome states that cognitive functions other than memory are relatively spared (Bodani et al., 2009), comprehensive neuropsychological testing may still reveal subtle deficits, most notably in visuo-perceptual functions and abstraction ability, provided that the performance on standard intelligence tests, i.e. those assessing crystallised intelligence, remain overall stable. In general, besides amnesia, it is the moderate to severe deficits in the executive functions that are most prominent. The patient population diagnosed with Korsakoff's syndrome is, however, very heterogeneous (Cutting, 1978). For one, it comprises patients with the classical syndrome that is associated with isolated amnesia and a prognosis that prevents them from

leading an independent life. In this group the syndrome typically presents acutely. The group with a gradual onset usually displays a greater array of cognitive impairments along with the amnesia. Moreover, some of these patients may in the course of time even show improvement in their cognitive abilities. Together with the results presented by Jacobson and Lishman (1987), who also noted a heterogeneous range of symptoms within the syndrome, these findings warrant the conclusion that patients with Korsakoff's syndrome present with varying degrees of cognitive decline, specifically in executive functioning, but other deficits may also occur. Still, in clinical practice the syndrome seems to be diagnosed more often than is strictly justified (e.g. in cases with mild memory problems rather than the required amnesic syndrome). It is, moreover, important to keep in mind that patients with Korsakoff's syndrome not only have the characteristic lesions in the diencephalon caused by vitamin deficiency, but also suffer from the effects of prolonged exposure to the neurotoxic mechanism of alcohol as such, resulting in cerebral atrophy in other parts of the brain.

Alcohol-related dementia

The distinction between a diagnosis of Korsakoff's syndrome and that of alcoholic dementia is a difficult one. The increased risk of dementia in older adults may pose a dilemma here, particularly in differential diagnoses in older patients with a lengthy history of alcohol abuse. Alcoholic dementia is a syndrome characterised by memory loss and a decline in intellectual capacity of such severity to hamper daily functioning that can be fully attributed to the toxic effects of alcohol on the brain. The rationale of alcoholic dementia as a diagnosis has been the subject of debate for years because validated clinical, neuropathological and radiological criteria are lacking. As opposed to other expressions of dementia, in alcoholic dementia no distinctive medical explanatory model exists. In other words: it has no specific underlying disease or unambiguous pathophysiological process or neuroanatomical substrate. It therefore makes little sense to denote alcohol-induced dementia as a separate illness. For this reason the broader term of alcohol-related dementia (ARD) has been introduced to describe a wider spectrum of alcohol-related cognitive deficits. The current diagnostic criteria for ARD are chiefly based on clinical grounds. Although they did not formulate formal criteria for a definite diagnosis of ARD, for a diagnosis of 'probable' ARD, Oslin, Atkinson, Smith, and Hendrie (1998) proposed clinical diagnosis of dementia, persisting for a minimum of 60 days after the most recent exposure to alcohol, a preceding history of excessive

alcohol use beyond 5 years, with a consumption of 35 and 28 standard units of alcohol per week for men and women, respectively. In contrast to other types of dementia, in ARD the cognitive decline does not progress with abstinence, while partial reversibility is even possible (Goldman, 1983). This latter phenomenon is highly relevant to the differential diagnosis of dementia syndromes. As a syndromal diagnosis, however, ARD may well contribute to the explanations of the incidence of severe cognitive impairments in individuals with a long-term history of alcohol abuse. The alcohol dependency may add to the damage already incurred through Alzheimer's disease or a vascular dementia, for instance. Like smoking, diabetes mellitus and genetic factors, alcohol abuse can then be taken into account in a causal model for individual patients (see e.g. Gupta and Warner, 2008).

Conclusion

Prolonged alcohol use may cause substantial damage to the brain, potentially producing a cognitive decline that may range from mild deficits to a dementia. If the alcohol abuse coincides with poor nutritional patterns, a resultant vitamin B1 deficiency may cause Korsakoff's syndrome, with severe amnesia and executive dysfunction. Delineating cognitive deficits resulting from alcohol use, Korsakoff's syndrome or alcohol-related dementia may be difficult in clinical practice, given that for all the conditions described clear biomarkers are as yet lacking. Thus, people who chronically drink excessive amounts of alcohol may possibly also be predisposed to executive problems (e.g. disinhibition, from which alcohol abuse may result) and at higher risk of cerebrovascular complications. Moreover, the abnormalities in the mammillary bodies in Korsakoff's syndrome cannot be easily detected by conventional brain imaging techniques. Finally, alcohol-related dementia is a syndromal diagnosis without a discrete neuroanatomical substrate.

Consensus on the clinical criteria of the syndromes discussed in this chapter also varies. If a patient is diagnosed based on the DSM, the emphasis lies on amnesia, even though Korsakoff's patients frequently also present with serious executive deficits, which, in the previous DSM-IV criteria, are insufficiently reflected (Van Oort & Kessels, 2009). In the DSM-5 the label 'Alcohol-induced Major Neurocognitive Disorder' also indicates that alcohol-induced deficits may not be limited to memory impairment (APA, 2013). As to alcohol-related dementia, it needs to be stressed that the criteria proposed by Oslin et al. (1998) have never been widely adopted. Nevertheless, in patients with a known or suspected history of alcohol abuse a sound assessment of their cognitive impairment and psychological dysfunction is always to be recommended.

Weighing the results of these tests with imaging data and findings from physical examinations may then help produce an explanatory model that can account for the cognitive deficits of the individual patient while taking the potential role of alcohol into account.

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3

CHAPTER

The RBMT as a measure of everyday memory in patients with Korsakoff's syndrome

Adapted from:

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Abstract

The existing test batteries assessing memory deficits in patients suspected of Korsakoff's syndrome have the disadvantage that they do not address the patients' everyday memory performance. The Rivermead Behavioural Memory Test (RBMT) is designed to assess memory problems in everyday contexts in patients with a brain disorder. Here, results on the RBMT are presented that were obtained in a large sample of known Korsakoff patients. Specifically, this paper focuses on the RBMT subtest profile to examine its feasibility in clinical practice.

Introduction

Patients with Korsakoff's syndrome constitute a special group within general psychiatric hospitals. Their cognitive deficits, with memory impairment being the most prominent, are the cause of considerable confusion in non-Korsakoff patients, while the Korsakoff patients are unable to correctly interpret the behaviours of their fellow patients. This mutual incomprehension, which recurrently escalated into fierce clashes and had a detrimental effect on the treatment of both patient groups, prompted some of these hospitals to create dedicated (residential) units for Korsakoff patients. The separate treatment facilities were found to have positive effects on various aspects of the patients' cognitive abilities and social behaviour (Ganzevles et al., 1994). In the Netherlands, this increased attention to the position of patients with Korsakoff's syndrome has also prompted attempts to improve the diagnostic procedures for this particular patient group, given that the DSM-IV diagnosis of 'alcohol-induced persisting amnestic disorder' (291.10) does not allow the nature, scope and severity of the cognitive deficits to be determined (APA, 2000).

The DSM-IV criteria of alcohol-induced persisting amnestic disorder are:

- Memory disturbance as manifested in an impairment in the ability to learn new information or the inability to recall previously learned information;
- The memory disturbance causes significant impairment in social or occupational functioning and a significant decline in the level of previous functioning;
- The memory disturbance does not exclusively occur during the course of a delirium or a dementia and persists beyond the usual duration of substance intoxication or withdrawal;
- There must be evidence from the history, physical examination or laboratory findings that the memory disturbance is directly related to physiological consequences of alcohol.

Besides the memory deficits, most Korsakoff patients also have serious problems planning and organising their behaviour, are themselves not or only marginally aware of their illness, and often show a lack of initiative as well as a lack of interest in social interaction. The DSM-IV classification of alcohol-induced persisting amnestic disorder hence also fails to take these symptoms into account in its description of Korsakoff's syndrome. In describing the diagnosis 291.1 as an alcohol-induced major neurocognitive disorder, amnestic-confabulatory type, persistent, the DSM-5 now gives room for more impaired cognitive domains than just memory (APA, 2013).

In 1992 the Dutch Korsakoff Foundation took the initiative for the development of a neuropsychodiagnostic procedure to help distinguish patients with Korsakoff's

syndrome from (chronic) alcoholics (Huijsman et al., 1992). Driven by the need for a theory-based neuropsychological test battery, Ganzevles and colleagues (1993) next composed the neuropsychological test battery for Korsakoff's syndrome designed to identify and quantify the deficits typically seen in patients suffering from alcohol-related Korsakoff's syndrome.

Both the procedure proposed by the Korsakoff Foundation and the Ganzevles et al. test battery were composed of standard neuropsychological tests and experimental material, and as such less suitable to gauge the performance of activities of daily living. Traditional test batteries do allow predictions of the probability of problems in everyday functioning, but are not specific as to their nature and scope (Wilson, 1993). With targeted treatment and rehabilitation in mind, it is especially relevant that assessments provide a reliable prediction of the problems patients may be facing at home or in learning or occupational settings. All this preferably, as Wilson (1993) poses, expressed in language and translated into activities that are both understandable and relevant to the patient and his or her family. In essence, this is referred to in the literature as ecologically validity (Hart & Hayden, 1986).

In the context of their memory research, Wilson et al. (1985) developed the Rivermead Behavioural Memory Test (RBMT), a test battery designed to detect everyday memory problems and monitor changes over time (e.g. during and after treatment), for which purpose four parallel versions were designed. Both test-retest and interrater reliability proved to be high. The RBMT thus appeared an ecologically valid measure to capture everyday memory deficits (Wilson et al., 1989). A Dutch adaptation of the test (Van Balen & Groot Zwaafink, 1987) soon became available, followed by the norm scores for the Netherlands and Belgium (Flanders) (Van Balen & Wimmers, 1992).

The RBMT consists of 12 standardized subtests analogous to everyday tasks that are administered and scored as regular neuropsychological tests: remembering a name with a face, a route (immediate and delayed recall), a story (immediate and delayed recall), an appointment, recognising pictures and faces, remembering to ask for a hidden personal belonging and remembering where the item was put, and orientation questions. Unlike many memory tests requiring the respondent to memorise and reproduce lists of words or complex figures, with the RBMT patients actually sense that their memory is being tested because the items are much truer to life.

The available Dutch normative data (Van Balen & Wimmers, 1992) do not allow discrimination among the various alcohol-related syndromes, such as patients with a (then current DSM III-R) diagnosis of alcohol-induced amnestic disorder (291.10), alcohol-related dementia (291.20), alcohol dependence (303.90) and alcohol abuse (305.00) pooled into one sample in the Dutch

norm study. A critical discussion of the RBMT can be found in Bouma et al. (2012).

In clinical practice, people with an alcohol problem are commonly found to present with memory impairment. For effective treatment it is crucial to be able to determine the severity of the memory deficits and, also based on the outcome, find support for the diagnosis of Korsakoff's syndrome; put differently, it is of the essence to be able to establish whether, as a family doctor put it, "his patient is well on the way to developing Korsakoff's syndrome or simply drinks too much." To this end, we have administered the RBMT in a large group of diagnosed Korsakoff patients.

Method

The clinical sample consisted of 322 inpatients with Korsakoff's syndrome residing in the Korsakoff clinic of the Vincent van Gogh Institute in Venray, the Netherlands. All patients fulfilled the DSM-IV criteria of alcohol-induced persistent amnesic disorder (291.10), as established by neurological, psychiatric and neuropsychological examination. Patient characteristics are given in Table 1. Educational level was determined according to the revised Verhage system (Duits & Kessels, 2006) where 1 represents the lowest (less than primary school) and 7 the highest level (academic degree). Intelligence was assessed by means of the Dutch adaptation of the Wechsler Adult Intelligence Scale (Stinissen et al., 1970) or the Groningen Intelligence Test (Luteyn & Van der Ploeg, 1983). Premorbid cognitive functioning was assessed using the Dutch Adult Reading Test (Schmand et al., 1992). Version 1A of the RBMT was administered to all patients within 6 weeks of their admission to the clinic.

Results

All 322 patients were able to complete the full RBMT-1A. The test has three scoring methods: raw, screening, and standard profile scores. The screening score is based on an 'all-or-nothing' principle, where errorless performance on each of the 12 subtests is awarded 1 point and all other achievements 0 points, with a maximum score of 12. The standard profile score is based on the raw score, where the raw score for each item is compared to the norm score, with 2 reflecting normal, 1 borderline and 0 abnormal scores, with a maximum score of 24. Table 2 lists the mean outcomes for the three scoring methods, together with their standard deviations.

Table 1 Characteristics of Korsakoff patients

	Male N=240	Female N=82	Total N=322
Age in years (Mean \pm SD)	51.4 (8.6) range=29-73	51.6 (7.5) range=35-66	51,4 (8,3) range=29-73
Level of education (1-7)	3.7 (1.5)	3.9 (1.2)	3,8 (1,4)
WAIS - IQ	94.1 (15.7) n=158	95.2 (17.0) n=41	94,4 (15,9) n=199
GIT - IQ	98.8 (15.2) n=78	90.1 (10.9) n=41	95,8 (14,4) n=119
NLV - IQ	96.4 (13.7) n=163	94.8 (13.8) n=61	95,9 (13,7) n=224

Table 2 Means and standard deviations of raw scores, standard profile scores and screening scores (N=322)

RBMT-items	Raw score		Standard Profile score		Screeningscore	
	Mean	SD	Mean	SD	Mean	SD
First name	0.52 (2)	0.82	}0.26	0.67	0.21	0.41
Second name	0.52 (2)	0.84	}		0.23	0.42
Belongings	2.34 (4)	1.20	0.67	0.75	0.23	0.42
Appointments	0.42 (2)	0.63	0.42	0.63	0.07	0.26
Picture recognition	7.31 (10)	2.53	0.59	0.81	0.21	0.41
Story recall, immediate	3.84 (21)	2.12	0.72	0.77	}0.08	0.28
Story recall, delayed	1.28 (21)	1.62	0.46	0.70	}	
Face recognition	3.47 (5)	1.52	0.91	0.85	0.32	0.47
Route, immediate	3.94 (5)	1.04	1.06	0.83	0.37	0.48
Route, delayed	3.35 (5)	1.31	0.72	0.80	0.21	0.41
Messages, immediate	2.44 (3)	0.76	}0.76	0.85	0.27	0.45
Messages, delayed	1.87 (3)	1.02	}			
Orientation	6.26 (4)	1.92	0.40	0.67	0.10	0.30
Date	0.29 (1)	0.46	0.76	0.88	0.30	0.46

In Tables 3 and 4 the screening and standard profile scores are compared to the cut-off scores and the interpretations of the resulting categories as proposed in the second supplement to the RBMT. Evaluation of the screening and standard profile scores reveals that 95.3% and 97.6% of the patients are moderately to severely impaired, respectively. As was to be expected, none of the patients achieved the norm or the maximum score with either rating. As to the difference between the Dutch and English normative scores, also obvious in our tables, Bouma et al. (1998) already suggested that this deviation may be explained by the Dutch 'normals' having been recruited among participants of memory training courses, rendering the sample less representative of the target population.

Table 3 Distribution of Screening Scores of Korsakoff patients (N=322) versus normal controls < 70 jaar with English (Wilson e.a., 1989) and Dutch normative data (Van Balen & Wimmers, 1992)*

Score	Korsakoff patients Cum.%	Class	English Cum.%	Dutch Cum.%
0	22.0	severe		0.8
1	37.9	impaired		1.6
2	53.4			2.4
3	68.6			2.4
4	80.1	moderate		4.0
5	88.5	impaired		6.4
6	95.3			9.6
7	98.1		4.3	21.6
8	99.7	mild	11.1	45.6
9	100	impaired	17.1	64.0
10			40.2	80.0
11		normal	67.5	98.4
12			100	100

* Adapted from Bouma et al. (2012)

Table 4 Distribution of the Standard profilescore of Korsakoff patients (N=322) versus normal controls < 70 jaar with English (Wilson e.a., 1989) and Dutch normative data (Van Balen & Wimmers, 1992)*

Score	Korsakoff patients Cum. %	Class	English Cum. %	Dutch Cum. %
0	3.7			
1-5	36.3	severe		0.8
6	43.5	impaired		1.6
7-9	63.4			2.4
10-11	76.4			2.4
12-13	82.0	moderate		3.2
14	89.8	impaired		4.0
15	94.1			7.2
16	96.9		0.9	8.0
17	98.4		3.4	10.4
18	99.4	mild	5.1	16.0
19	99.7	impaired	11.1	26.4
20	100		19.7	35.2
21			31.6	58.4
22		normal	41.9	72.8
23			67.5	87.2
24			100	100

*Adapted from Bouma et al. (2012).

Interpretation of the results

Despite its three scoring procedures, it is unfortunate that, due to their nature, much information about the performance on individual items is lost in the RBMT. As an illustration, in the 'pictures' and 'faces' tests, erroneously recognised images are deducted from correctly identified ones, obscuring the respondent's actual performance. In clinical practice it is especially important to be able to establish the patient's strengths and weaknesses as precisely as possible in order to tailor subsequent treatment, while it is exactly this clinically relevant information that is lost due to the scoring method. Accordingly, in order

Table 5 Frequencies (in %) of screeningscores and standard profile scores per item (N=322)

RBMT-items	Screeningscores		Standard profile scores		
	0	1	0	1	2
First name	78.6	21.4}	86.0	1.6	12.4
Second name	76.7	23.3}			
Belongings	82.3	17.7	49.7	33.2	17.1
Appointments	92.5	7.5	65.5	27.0	7.5
Pictures recognition	79.2	20.8	61.5	17.7	20.8
Story recall, immediate}	91.6	8.4	48.1	32.0	19.9
Story recall, delayed}			66.1	22.1	11.8
Face recognition	68.0	32.0	41.3	26.7	32.0
Route, immediate	63.0	37.0	31.0	31.7	37.3
Route, delayed	78.6	21.4	49.7	28.6	21.7
Messages	72.7	27.3	50.9	21.7	27.4
Orientation	89.8	10.2	69.9	19.9	10.2
Date	70.2	29.8	53.1	17.7	29.2

to evaluate the patients' actual performance in more detail, outcomes on the various subtests will be discussed separately below.

– *Remembering a name*: Over a fifth of the Korsakoff patients was able to correctly reproduce the first name when shown the photograph again. With some help (first letter was given) a few more patients succeeded in recalling the name. The other patients offered a wrong or no name. Almost a quarter spontaneously recollected the last name, with the first letter prompting only a few to also come up with the correct name. The others offered a wrong or no last name. Few patients succeeded in retrieving both names unprompted. Some tried to gloss over their inability with statements in the following vein: "I got confused by the story," "I didn't pay any attention to the name" or simply "I haven't seen this photo before."

– *Belongings*: Many patients confused this assignment with the appointment task. A small number of the patients managed to recall both the object and the place where it was hidden without prompt. Approximately a third needed a pointer for the object or its location. Closer inspection of the data reveals that almost half of the patients were able to recollect the right location unprompted, while this was a third for remembering the object.

– *Appointment*: This proved the most difficult task for our Korsakoff patients. About a quarter did not respond in any way to the alarm clock requiring them to ask the examiner the set question. When asked about this omission, most offered more or less standard reactions like “I thought it was a telephone ringing” or “Was that meant for me?” Quite a few patients confused this assignment with the ‘belonging’ task. To a lesser degree, there was some interference with, among other items, the name and message tasks. A small group of patients was capable of spontaneously reproducing the verbatim question, while a quarter remembered they needed to ask a question but failed to recollect its content.

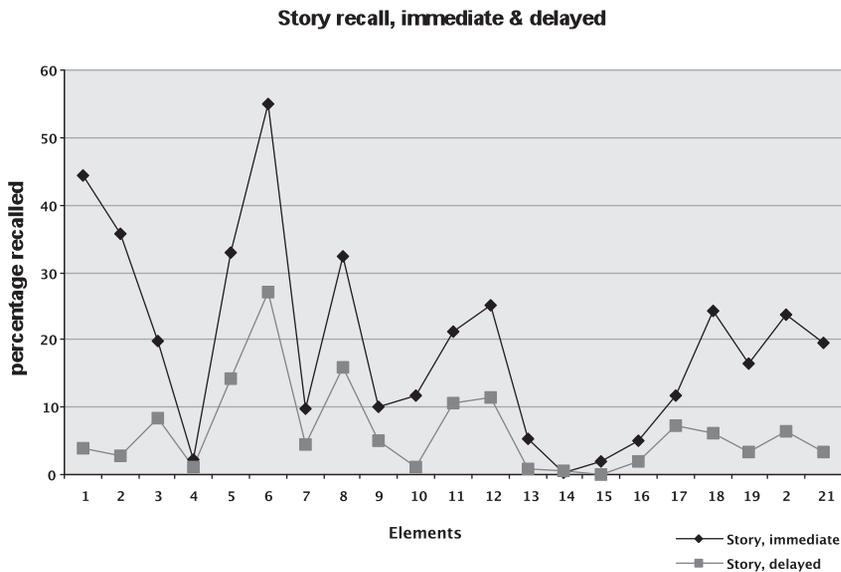
– *Picture recognition*: For the raw score of this subtest, the number of incorrectly recognised pictures is subtracted from that of the correctly recognised images, which implies that the resultant scores no longer reflect true performance. As an illustration, a raw score of 7 may yield a total of 0 for both the screening and the profile scores when a respondent has correctly recognised only seven pictures without erroneously recognising any of the other pictures (i.e. false positive responses). Correctly recognising 10 pictures together with three false positives, however, produces the same scores. Remarkably, very few of the Korsakoff patients (1.86%) failed to recognise any of the pictures. A quarter succeeded in correctly recognising all pictures without any false positives.

– *Story recall*: More than any of the other items, the immediate and delayed recall of a short story provoked confabulation in some patients, which mostly consisted of a mixture of true elements and personal additions. “A girl had a pair of walking sticks, green walking sticks. Four men were standing near a window that they wanted to smash in. The police arrived. They wanted to arrest him. A boy had hidden a gun and shot an officer in the throat. That’s it.” In most cases the ‘invented’ elements from the direct recall reemerge in the delayed story, as is shown in the following example. The version in the direct recall condition reads “Bert Koster was arrested by the police on Monday because he had committed fraud at a Swiss bank and had beaten two men to death and injured a woman. He was sentenced to ten years, but because of exemplary conduct he only served two years,” which in the delayed recall has turned into “A young man was arrested and later sentenced to 11 years and because he had behaved in such exemplary fashion the sentence was reduced and he was released two years earlier.” The delayed recollections also recurrently show signs of interference from other test items: “The story of the alarm clock?”, “The appointment for next time?”

For comparison, this is the original Dutch story translated into English:

Bert/ Koster/, a security guard/, was shot and killed/ during a bank robbery/ in Zwolle/ last Monday./ The four robbers/ all wore masks./ One of the robbers had/ a sawn-off / shotgun./ Last night/, detectives/ were still going through/

the eye witness reports./ A police spokesman said:/ "He was a very brave man./ He chased/ the robbers,/ trying to stop them."



3

Figure 1 Profile of recalled elements of immediate and delayed story-recall

Only a few of our respondents succeeded in recalling a minimum of six salient elements of the story in the direct and four elements in the delayed recollection. Only one patient was unable to recall a single element in the direct reproduction. In the delayed reproduction, the number of patients that have no recollection of any story or cannot reproduce any of its content rises to nearly 40%. Figure 1 shows for each of the 21 sequential elements of the story the times (in percentages) it was partially or fully reproduced in the direct and delayed conditions. The figure allows the overall inference that when recalling the story immediately, the Korsakoff patient remembers: "Bert Koster, a security guard, was killed in a bank robbery by four robbers with a sawn-off shotgun. He went after the robbers and tried to stop them." Most of these details are mentioned in some sense or other in the delayed reproduction. What is most prominent is the failure to mention the seemingly salient element 'Bert Koster, a security guard' in the later reproduction. Other details of the story (was, Monday, detectives,

going through, last night) are rarely, or even never, mentioned, either in the direct or the delayed account.

– *Face recognition*: As with picture recognition, the raw score of this subtest is arrived at by subtracting the number of incorrectly recognised faces from the number of correct recognitions, again complicating the interpretation of the outcomes. A third of the Korsakoff patients recognised all faces without any false positives. Further analysis reveals that only 4.65% of the respondents failed to recognise a single face, with even very few (0.93%) not able to recognize any face correctly.

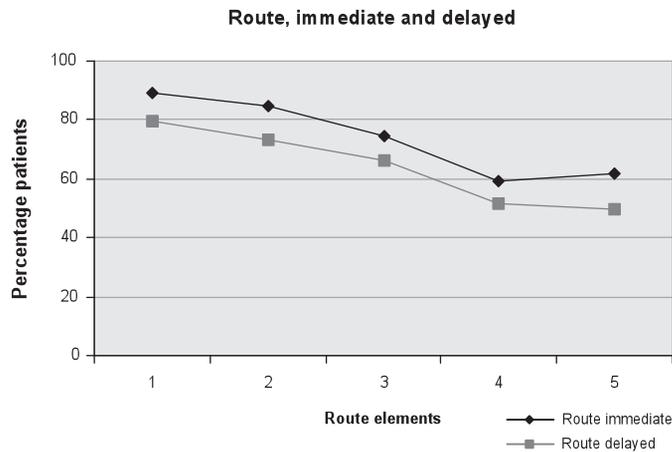


Figure 2 Profile of recalled elements of immediate and delayed route-recall

– *Route recall*: A good third of the patients successfully completed the route immediately following demonstration. In the delayed test, a fifth still walked the route without errors. Not all stages of the route were remembered equally well. Figure 2 depicts the decline in the course of the route and between the direct and delayed walks.

– *Message*: Both in the immediate and the delayed test, over a quarter of the patients spontaneously remembers to pick up the message when walking the route, and to deposit it in the correct spot. Also here, clinically relevant information is lost by performance scores for the separate components being pooled for the screening and standard profile scores. Looking at each subtest separately, we find that in the direct recall condition 58.1% took and delivered

the message without error and that 1.4% failed to remember the task all together, rendering any reminders futile. In the delayed condition, 39% showed an error-free performance, while 10.6% had no recollection of the assignment and did not benefit from directions. Sometimes patients could not recall where the message was to be left when walking the route upon demonstration, while they did remember the location in the delayed condition. Others spontaneously remembered to pick up the message in the delayed recall, whereas they failed to do so in the immediate recall, where they needed a cue.

– *Orientation*: This subtest, comprising nine, basic orientation questions, is completed without errors by as little as 10% of the patients, with 20% making at least one mistake. Also here, salient information is lost due to the scoring method. At the individual question level, all our patients (100%) were able to give their year of birth (i.e. they all knew their full date of birth); 76.02% managed to state their age; 81.87% knew the year ‘we’re living in’, with 77.78% and 70.76% succeeding in giving the month of the year and the day of the week, respectively. 74.85% knew the institute they were at, and 87.72% could state the city. Considerably more patients had difficulty producing the names of the current prime minister of the Netherlands and the president of the USA. 51.46% know the PM’s name, while the other patients have no idea or propose names of former PMs (e.g. Drees, Biesheuvel or Van Agt), with the latter apparently having made the most impression as he is mentioned most frequently. Quite a few patients (43.27%) knew the name of the current US president. The others failed to come up with a name or offered names of predecessors, with Nixon being by far the most frequently mentioned.

– *Date*: Almost a third of the patients gave the correct date and 17.7% were only one day off. The scores again fail to reflect the outcomes for the other patients. Scrutiny of those data revealed that 52.05% offered dates that were wrong by 2-20 days, 9.36% by 1-9 months, and 8.19% by 1-2 years. The most deviating dates are given by four patients who are wrong by as much as 5, 15, 19, and 20 years, respectively.

Discussion

With the present study we are in no way attempting to provide a memory theoretical framework for the amnesic deficits that we obtained in patients with Korsakoff’ syndrome using the Rivermead Behavioural Memory Test, nor did we seek to compare the outcomes with performance scores obtained with other memory tasks or with other patient populations. The most recurrent question in the clinical management of Korsakoff patients is whether patients

with alcohol abuse have objective memory deficits, and, if so, whether they have Korsakoff's syndrome. And in what domains do the amnesic problems manifest themselves most and to what magnitude? The data we have presented here may then serve as a frame of reference when trying to answer these kinds of questions. In doing so, it does need to be taken into account that our findings were obtained in clinically confirmed Korsakoff patients that had been newly admitted to our clinic for targeted treatment. The majority were referred by neurology or psychiatry departments of general hospitals, where they had been staying from several weeks to several months. A minority had been referred by an addiction clinic or a psychiatric hospital, with some patients being admitted to our clinic from their homes (e.g., referred by their general practitioner). Previous studies typically recruited 'chronic' Korsakoff patients from long-term residential settings, in contrast to our sample that consists of patients still undergoing treatment. As a result they showed more variety in terms of their levels of cognitive and executive functioning.

All too often, when alcoholics have problems with their memory, Korsakoff's syndrome as a diagnostic label is readily concluded. The data presented in Tables 3 and 4 may contribute to differential-diagnostic decision making. Using the data for the individual items of each subtest, a patient's profile as well as the magnitude of his or her memory deficits can be compared with the outcomes obtained in Korsakoff patients. Thus, if during an assessment consultation the patient is unable to give his correct date of birth, the suspicion of a different syndrome than Korsakoff's that is also associated with memory impairment may be justified, given our findings on this aspect. Does the patient perhaps suffer from a dementia, or is he underperforming due to confusion? The likelihood that a patient with Korsakoff's syndrome is unable to recognise a single face or picture correctly is very small, while such an outcome does help quantify the severity of the memory impairment.

These findings obtained in a sample of clinically confirmed Korsakoff patients using the Rivermead Behavioural Memory Test contribute to the clinical application of this test in patients with alcohol-use disorder.

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CHAPTER

A comparison between the RBMT and the CVLT

Revised version submitted:

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Assessment of Alcohol-Related Memory Deficits: a Comparison between the Rivermead
Behavioural Memory Test and the California Verbal Learning Test.



Abstract

Background: Neuropsychological assessment of memory disorders is an important prerequisite in the treatment of patients with alcohol-related cognitive disorders. Although many memory tests are available in clinical practice, a question remains which test is most appropriate for this purpose. Our study's goal was to evaluate the discriminative power of a standard memory test (the California Verbal Learning Test; CVLT) versus an ecologically valid everyday memory test (the Rivermead Behavioural Memory Test; RBMT) in patients with alcohol-use disorder. Included were 136 patients with Korsakoff's syndrome (KS), 73 alcoholics with cognitive impairment (CI) and 24 cognitively unimpaired alcoholics (ALC).

Results: Results showed that KS patients performed significantly lower on all RBMT and CVLT variables than CI patients. ALC patients performed significantly better than CI patients on only one RBMT subtest, and had significantly lower rate of forgetting and higher scores of free recall on CVLT.

Conclusion: Our findings indicate that a combination of RBMT subtests and CVLT indices can be used to to discriminate KS patients from CI and ALC patients. The RBMT could not significantly distinguish ALC from CI patients. However, both rate of forgetting and a comparison between free and cued recall testing on the CVLT showed the largest between-group differences.

Introduction

Long-term alcohol abuse may result in cognitive disorders. Although numbers vary in different publications, it is estimated that about half of the people seeking treatment for alcohol addiction have cognitive deficits (Rourke & Grant, 2009). Cognitive disorders may appear long before alcohol-induced neurological symptoms are visible and may have important negative consequences for treatment success and everyday functioning (Rourke & Grant, 2009). About 10% of people with alcohol addiction develop severe cognitive disorders, such as Korsakoff's syndrome (Rourke & Grant, 2009). Victor, Adams and Collins (1989) described this syndrome as 'an abnormality of mentation, in which memory and learning are affected out of proportion to other cognitive functions in an otherwise alert and responsive patient'.

Cognitive disorders can be the result of the direct effects of long-term alcohol abuse such as the toxic action of alcohol itself or the consequences of abrupt alcohol withdrawal, and by indirect effects of alcohol use like thiamine deficiency or liver cirrhosis (Bodani, Reed, & Kopelman, 2009). The cognitive disorders include memory deficits, visuo-spatial impairment, attention deficits and executive dysfunction, but the extent in which these domains are affected varies greatly. In some cases of chronic alcoholics, the severity of memory impairment resembles the deficits seen in alcoholics with Korsakoff's syndrome. This led Bowden (1990) to question the rigid neuropsychological distinction between non-Korsakoff and Korsakoff alcoholics, in line with the previously postulated continuity hypothesis, reflecting a continuum of cognitive impairment, ranging from normal at the one extreme to very severe deficits at the other, depending on the frequency, quantity and duration of alcohol intake (Ryback, 1971; Ryan & Butters, 1980). Also, Sullivan and Pfefferbaum (2009) showed a graded effect of structural deficits in the brains, ranging from mild or moderate in non-Korsakoff alcoholics, to severe in Korsakoff alcoholics.

In clinical practice it is important to distinguish patients with permanent alcohol-related cognitive deficits from patients that may show partial or full cognitive recovery. That is, the prognosis of non-Korsakoff alcoholics with cognitive disorders is favourable in the case of long-term abstinence (Wilson, 2011). This abstinence, combined with tailor-made treatment programs, generally results in improved cognitive functioning, leading to permanent abstinence and more successful everyday functioning (i.e. independent living). In contrast, alcoholics with Korsakoff's syndrome require a different therapeutic approach, that is, a treatment program that fits their severe memory disorders, improves their social functioning, and at best prepares them for living in a sheltered accommodation (Ganzevles, De Geus & Wester, 1994).

With targeted treatment in mind, it is important that neuropsychological assessment provides a reliable prognosis of the difficulties patients may encounter during rehabilitation, at home, or in occupational settings. A wide variety of neuropsychological tests is available to examine memory functioning, such as word-list learning tests like the California Verbal Learning Test (CVLT) or the Rey Auditory Verbal Learning Test (RAVLT). However, the ability of a standard memory test to predict everyday memory functioning (often referred to as ecological validity) has been questioned (Wilson, 1993). The Rivermead Behavioural Memory Test (RBMT) has been developed to detect everyday memory deficits and monitor changes over time (Wilson, Cockburn, Baddeley, & Hiorns, 1989). A direct comparison of a standard memory task and an ecologically valid memory test may provide insight into the applicability of these tests as potentially sensitive measures of everyday memory deficits in patients with alcohol-related cognitive disorders.

In the present study we compared the performance of three groups of patients with alcoholic Korsakoff's syndrome: patients with chronic alcoholism and cognitive complaints, and patients with alcoholism without cognitive impairment. We administered a standard memory task and an ecologically valid everyday memory test. We hypothesized that 1) both the group with alcoholic Korsakoff's syndrome and the group with chronic alcoholism and cognitive complaints differ significantly from the group without cognitive impairment on both tests, and that 2) the group with Korsakoff's syndrome would differ significantly from the mild impaired alcoholics on both tests. Furthermore we investigated which (sub)test contributes to a better discrimination between the three groups.

Materials and Methods

Participants

In this study, 233 alcoholic patients were included. All participants were inpatients of a psychiatric treatment facility in Venray, the Netherlands, specialized in neuropsychological assessment and treatment of patients with alcohol related cognitive impairments. 136 of the participants in this study were diagnosed with Korsakoff's syndrome (KS), 73 with alcohol related cognitive impairments (CI) not fulfilling the criteria for KS and 24 participants had a history of alcohol abuse, but no cognitive impairments (ALC). The KS patients fulfilled the DSM-IV-TR (APA, 2000) criteria for alcohol-induced persisting amnestic disorder (code 291.1) for which a memory deficit had to be present, that results in severe deficits in social functioning, in the absence of delirium or dementia, with a history of alcohol-abuse disorder. In addition, the criteria for

alcoholic Korsakoff's syndrome (Kopelman, 2002) had to be met which included evidence for a history of Wernicke encephalopathy, confabulation behavior and history of malnutrition or thiamine deficit. The CI group had a history of chronic alcoholism (DSM-IV-TR code Alcohol Dependence, 303.90) and fulfilled the DSM-IV-TR criteria for cognitive disorder not otherwise specified (DSM-IV-TR code 294.9). The ALC group had a history of chronic alcoholism (DSM-IV-TR code Alcohol Dependence, 303.90), but no cognitive impairments. All diagnoses were made using a multidisciplinary approach supported by medical history, psychiatric assessment, neuropsychological testing covering all major cognitive domains and neuroradiological findings, and all patients had been abstinent for alcohol for at least six weeks. None of the patients had any evidence for brain abnormalities that could account for their condition apart from atrophy or white-matter lesions associated with the chronic alcohol abuse. None of the participants met the proposed criteria for alcohol-related dementia (Oslin, Atkinson, Smith, & Hendrie, 1998) and none of the participants had any hearing problems, language or communication deficits, or visual agnosia that could confound the performance on memory tests.

The mean age of the sample was 54.6 years (range 35-77). Table 1 presents the demographic information regarding the three groups. One-way analysis of variance did not reveal significant age differences ($F(2,230) = 2.01, p = 0.14$) between patients with KS, CI or ALC, or significant group differences on a premorbid intelligence measure ($F(2,224) = 0.07, p = 0.93$), the National Adult Reading Test (NART). Also, no significant group differences were found on sex distribution ($H(2) = 1.91, p = 0.39$) or educational level ($H(2) = 0.61, p = 0.74$).

Table 1 Demographic Information of Patients with Korsakoff's Syndrome, Cognitive Impairments and Alcohol Abuse.

	Korsakoff's syndrome	Alcohol related cognitive impairments	Alcohol abuse
N	136	73	24
Age	55.20 (7.72) Range = 35-75	54.49 (7.50) Range = 40-77	51.79 (8.23) Range = 35-64
Sex (N)			
Male	104	50	19
Female	32	23	5
Educational level	Mode = 4 Range = 1-7	Mode = 4 Range = 1-7	Mode = 4 Range = 2-7
NART IQ	95.09 (14.66)	95.85 (13.45)	95.10 (15.40)

Note: Educational level was scored using 6 categories in accordance with the Dutch educational systems (1 = less than primary school; 7 = academic degree); NART = National Adult Reading Test.

Materials

Rivermead Behavioural Memory Test

The Rivermead Behavioural Memory Test (RBMT) was designed to be an ecologically valid everyday memory test (Wilson et al., 1989). A Dutch version of the RBMT has been developed by Van Balen, Westzaan, and Mulder (1996), which was used in this study. By mapping memory abilities essential for adequate daily functioning, the RBMT aims to provide meaningful information regarding therapy (Van Balen et al., 1996; Wilson, 1987). The RBMT consists of fourteen subtests, measuring a variety of every-day memory skills: remembering a name (first and second name), a hidden belonging, an appointment, a news story (immediate and delayed recall), a route (immediate and delayed recall), delivering a message (immediate and direct recall), recognizing pictures and faces, orientation in time and place and recollection of the date. The subtests encompass verbal memory, visual memory and visuospatial memory in immediate, delayed and prospective (recollection of something that needs to be done) conditions. Both intentional as well as incidental learning is required and both cued and uncued recall tests are used. For every subtest a raw score, standardized profile score and screening score was obtained. Raw scores range between 0 and 21, with a maximum total score of 93. Raw scores have been converted into standardized profile scores and screening scores using the test's manual. Standardized profile scores range from 0 to 2 per subtest (reflecting an impaired, borderline or unimpaired performance respectively), with a maximum total score of 24 (Van Balen et al., 1996; Wilson et al., 1989).

California Verbal Learning Test

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was developed to measure impairments in learning and remembering of new verbal information in patients with acquired brain damage during four stages of learning: encoding, consolidation, retrieval and recognition. The Dutch version (Mulder, Dekker & Dekker, 1996) was used in the current study. The CVLT involves the oral presentation of a sixteen-word (shopping) list with items from four semantic categories (List A) over five immediate-recall trials. An interference list (List B) is also presented for one immediate-recall trial, followed by short-delay free-recall and cued-recall tests of list A, a long-delayed free recall and cued recall of list A and a recognition memory trial. The indices obtained include the level of correct recall over the various trials, learning strategies (e.g., semantic or serial clustering) and error types (e.g., intrusions and perseverations). In this study, the following measures were included: total score of list A (over five trials), rate of learning (trial 5 minus trial 1), rate of forgetting (trial 5 minus

long-term free recall), short-term free recall, short-term cued recall, long-term free recall, long-term cued recall and recognition (hits minus false positives).

Procedure

All participants were examined by a psychiatrist, neurologist, general practitioner and a neuropsychologist, and the medical history, and the history of alcohol abuse were reviewed. A complete neuropsychological examination was conducted after a period of minimally six weeks of abstinence of alcohol. The neuropsychological evaluation included tests of intellectual functioning, estimation of premorbid intelligence level, assessment of memory, and appraisal of executive functions and attention. The tests used in this study were part of this more extensive test battery. Patients were individually tested during two test-sessions on separate days. Testing was performed by trained assessors and took about three hours per session. Consensus on diagnoses was reached in a multidisciplinary meeting where all data from laboratory, neuroimaging, psychiatric and neurological investigation, clinical observations and neuropsychological assessment were evaluated.

4

Statistical analyses

We performed a multivariate analysis of variance (MANOVA) to investigate whether there are significant differences between the three groups: patients with KS, CI and ALC, on all fourteen raw scores of the RBMT and eight CVLT variables. The CVLT recognition scores of fifteen patients with KS and ten patients with CI were missing because of refusal of the patients to complete the test. These scores were replaced with the mean recognition score per group. To explore the relative contribution of the CVLT and RBMT variables to group discrimination, we performed a discriminant analysis that provides information about the underlying dimensions of the data (Field, 2009). The predictive power of the CVLT and RBMT for distinguishing KS, CI and ALC was evaluated by computing two Receiver Operating Characteristic (ROC) curves: one for discriminating between KS and CI and one for differentiating CI from ALC. For data-reduction purposes, a global index of both tests was used in the ROC-curve, that is, the total score (over five trials) of the CVLT and the total standardized profile score of the RBMT. The area under the curve (AUC) was computed to evaluate the predictive power of the tests.

Results

Table 2 shows the results of a multivariate analysis of variance (MANOVA), performed to investigate differences between patients with KS, CI and ALC on fourteen RBMT variables and eight CVLT variables. A significant main effect for group was found on the RBMT and CVLT variables ($F(44, 420) = 5.04, p < 0.05$). Post-hoc comparisons were performed on the RBMT subtests and CVLT indices using Dunnett's test, with patients with CI as reference group. As expected, patients with KS performed significantly lower on all RBMT and CVLT variables (see Tables 2

Table 2 Mean scores and Standard Deviations of RBMT Raw Scores of Patients with Korsakoff's Syndrome, Cognitive Impairments (reference group) and Alcohol Abuse.

	Korsakoff's syndrome N=136	Alcohol related cognitive impairments N=73	Alcohol abuse N=24
Total Standardized Profile Score	8.86 (5.48)	17.42 (4.71)	18.79 (3.85)
Total Screening Score	3.29 (2.80)	7.79 (2.66)	8.29 (2.31)
Raw Scores per Subtest			
First Name	0.54 (0.82)***	1.45 (0.88)	1.67 (0.70)
Second Name	0.61 (0.89)***	1.63 (0.76)	1.63 (0.71)
Belongings	2.53 (1.22)**	3.03 (1.05)	3.75 (0.53)*
Appointments	0.72 (0.78)***	1.38 (0.83)	1.42 (0.65)
Picture Recognition	7.71 (2.42)***	9.37 (1.32)	9.67 (0.92)
Story IR	3.78 (2.00)***	6.69 (3.24)	5.76 (2.87)
Story DR	1.59 (1.76)***	4.76 (3.10)	4.15 (2.33)
Face Recognition	3.98 (1.34)***	4.64 (0.70)	4.71 (0.55)
Route IR	3.64 (1.41)***	4.51 (0.75)	4.63 (0.77)
Route DR	3.21 (1.67)***	4.38 (0.97)	4.46 (0.83)
Messages IR	2.21 (0.94)***	2.67 (0.53)	2.79 (0.42)
Messages DR	1.84 (1.06)***	2.62 (0.64)	2.71 (0.55)
Orientation	6.74 (2.04)***	8.55 (0.83)	8.46 (0.66)
Date	0.42 (0.50)***	0.79 (0.41)	0.92 (0.28)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: RBMT= Rivermead Behavioural Memory Test, IR= Immediate recall, DR= Delayed recall.

and 3) than patients with CI. Patients with ALC achieved a significantly higher score than patients with CI on the RBMT subtest Belongings, and obtained a significantly lower rate of forgetting and significantly higher scores on both immediate and delayed free-recall testing on the CVLT (see Tables 2 and 3).

Table 3 Mean Scores and Standard Deviations of CVLT scores of Patients with Korsakoff's Syndrome, Cognitive Impairments (reference group) and Alcohol Abuse.

		Korsakoff's syndrome N=136	Alcohol related cognitive impairments N=73	Alcohol abuse N=24
List A	<i>Total Score</i>	25.58 (8.18)***	40.22 (11.28)	45.17 (13.09)
	<i>Rate of Learning</i>	2.01 (1.89)***	4.11 (2.38)	3.79 (1.93)
	<i>Rate of Forgetting</i>	3.96 (2.41)***	2.11 (2.40)	0.58 (2.08)*
Short Term Recall	<i>Free Recall</i>	1.74 (2.50)***	7.07 (3.41)	9.08 (4.10)**
	<i>Cued Recall</i>	4.85 (2.92)***	8.92 (3.27)	10.08 (3.30)
Long Term Recall	<i>Free Recall</i>	1.88 (2.87)***	7.52 (3.93)	9.67 (3.98)*
	<i>Cued Recall</i>	4.38 (3.02)***	8.73 (3.54)	10.38 (3.16)
Recognition		26.18 (8.19)***	32.67 (7.94)	34.88 (9.05)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: CVLT = California Verbal Learning Test.

Discriminant analysis revealed two discriminant functions. The first function explained 89.3 % of the variance, canonical $R^2 = 0.56$, whereas the second function explained only 10.7 %, canonical $R^2 = 0.13$. In combination, these discriminant functions significantly differentiated the three patient groups, Wilks' Lambda = 0.38, $\chi^2(44) = 210.77$, $p < 0.05$, but removing the first function indicated that the second function did not significantly differentiate the three groups, Wilks' Lambda = 0.87, $\chi^2(21) = 30.97$, $p = 0.07$. The canonical structure, i.e., the correlations between the RBMT and CVLT variables and the discriminant functions are shown in Table 4. Coefficients higher than 0.40 were considered significant. The correlations between outcomes and the first discriminant function revealed that the CVLT variables contributed more to the prediction of group membership than the RBMT variables. Of the former, the most discriminating variables were free and cued recall, CVLT total score, and CVLT's rate of forgetting and rate of learning. The best discriminating RBMT variables were story recall, remembering a name, orientation and date. The correlations

between outcomes and the second discriminant function indicated that, on top of the contribution of the first function, the subtest Story Recall of the RBMT had an additional contribution to the prediction of group membership.

Table 4 Canonical Variate Correlation Coefficients between the CVLT and RBMT Variables and the Discriminant Functions.

Test variables	Discriminant Function 1	Discriminant Function 2
1. CVLT Short term FR	0.87	-0.03
2. CVLT Long term FR	0.83	-0.04
3. CVLT Total score	0.72	0.01
4. CVLT Long term CR	0.67	-0.03
5. CVLT Short term CR	0.63	0.05
6. RBMT Story DR	0.55	0.48
7. RBMT Second name	0.53	0.28
8. RBMT First name	0.52	0.08
9. RBMT Orientation	0.47	0.29
10. RBMT Story IR	0.44	0.50
11. CVLT Rate of forgetting	-0.43	0.24
12. CVLT Rate of learning	0.42	0.33
13. RBMT Date	0.40	0.01
14. RBMT Messages DR	0.39	0.13
15. CVLT Recognition	0.38	0.00
16. RBMT Picture Recognition	0.38	0.09
17. RBMT Appointments	0.37	0.17
18. RBMT Route DR	0.37	0.15
19. RBMT Route IR	0.33	0.10
20. RBMT Belongings	0.29	-0.32
21. RBMT Messages IR	0.28	0.03
22. RBMT Face recognition	0.27	0.10

Note: CVLT= California Verbal Learning Test, RBMT= Rivermead Behavioural Memory Test, FR= Free Recall, CR= Cued Recall, IR= Immediate Recall, DR= Delayed Recall.

The discriminant function plot in Figure 1 showed that the first function discriminated patients with KS from patients CI and ALC, and the second function differentiated the patients with CI from patients with KS and ALC. However, the combination of the two functions appeared to be most effective in predicting group membership.

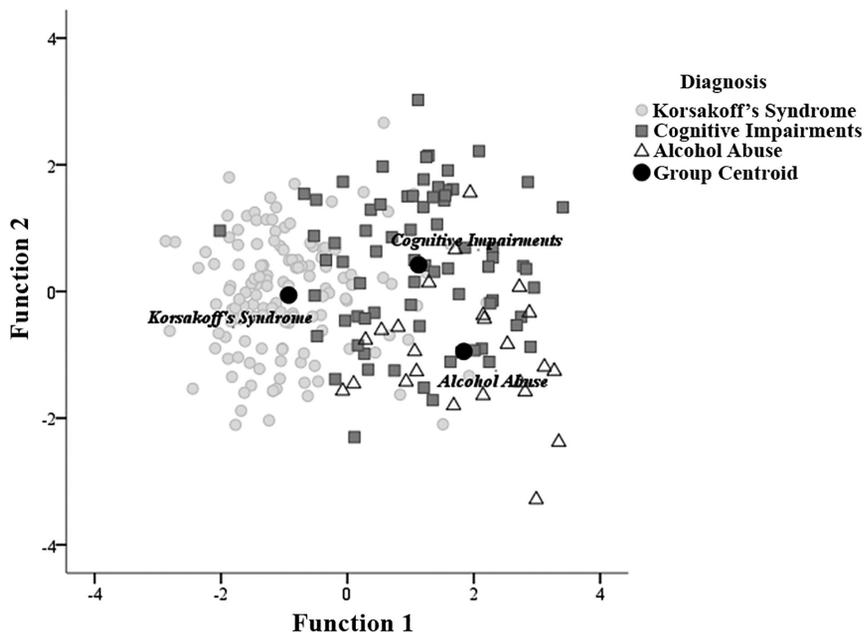


Figure 1 Graphical representation of variate scores for each patient, grouped by diagnosis

Figure 2 shows the ROC curves for distinguishing KS from CI. The AUC was 0.87 for the total standardized profile score of the RBMT (95% confidence interval 0.82-0.92, $p < 0.005$) and 0.86 for the CVLT total score (95% confidence interval 0.81-0.92, $p < 0.005$). These figures show that both the total standardized profile score of the RBMT, as well as the CVLT total score had significant and substantial predictive power in distinguishing KS from CI. In contrast, the ROC AUC for distinguishing CI from ALC (Figure 3) was 0.57 for the total standardized profile score of the RBMT (95% confidence interval 0.44-0.70, $p = 0.32$) and 0.60 for the

CVLT total score (95% confidence interval 0.47-0.74, $p= 0.13$), indicating that the tests had no significant predictive power for distinguishing CI from ALC.

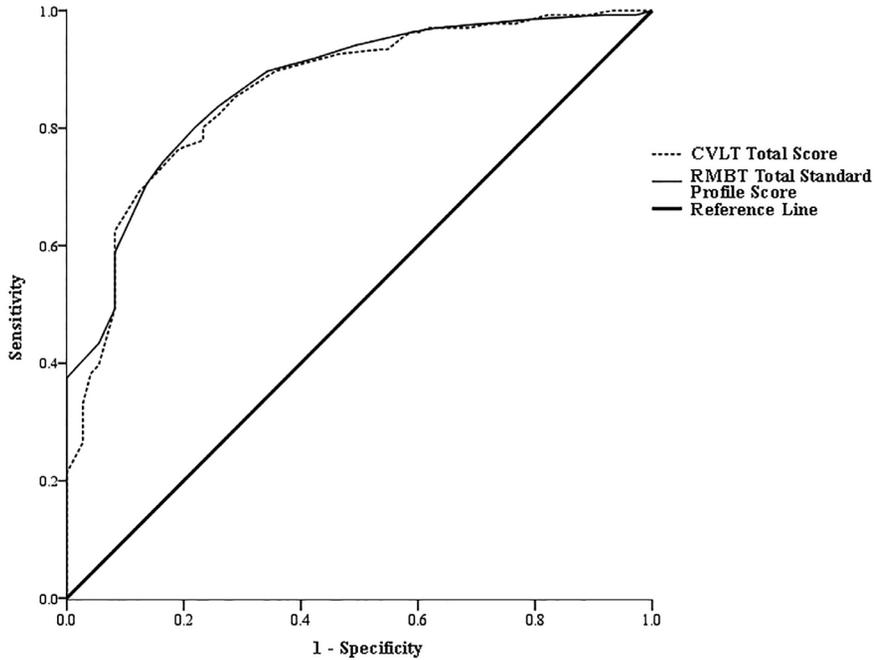


Figure 2 ROC-curve KS-CI: Predictive power of the total score of the California Verbal Learning Test and the total standard profile score of the Rivermead Behavioural Memory Test in distinguishing patients with Korsakoff's syndrome from those with cognitive impairments

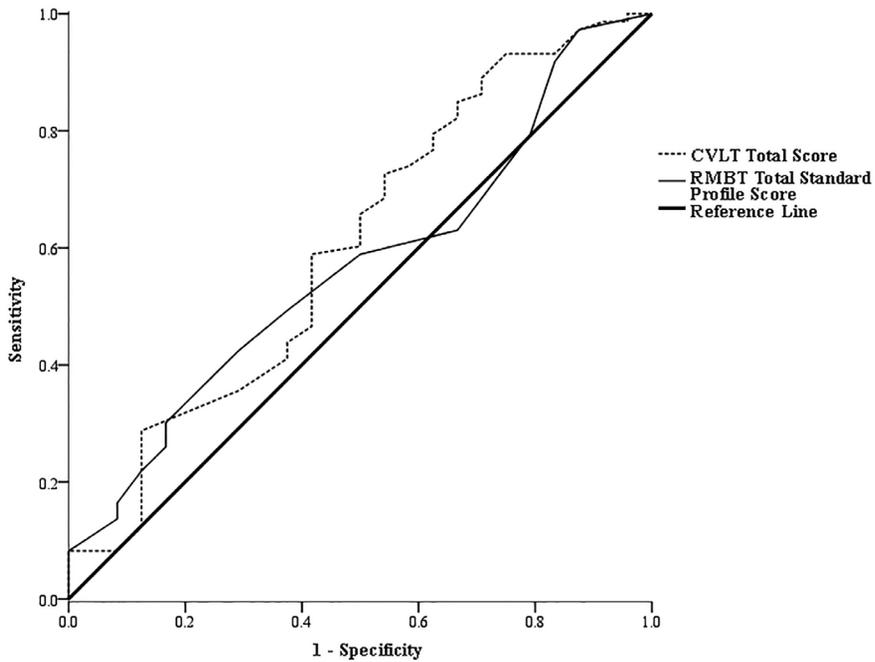


Figure 3 ROC-curve CI-AA: Predictive power of the total score of the California Verbal Learning Test and the total standard profile score of the Rivermead Behavioural Memory Test in distinguishing cognitive impairments from alcohol abuse

Discussion

This study aims to compare the performance of patients with Korsakoff's syndrome, alcoholic patients with moderate to mild cognitive deficits, and alcoholic patients with no cognitive dysfunctions, on a 'behavioral' test (RBMT) and a 'traditional' test (CVLT). As expected patients with KS performed significantly lower on all RBMT and CVLT variables than patients with CI. On the RBMT, ALC patients did not differ from the CI patient group, except for a significantly higher score on the RBMT subtest 'Belongings'. This finding is in

agreement with previous suggestions indicating that the RBMT is not sensitive for identifying more subtle memory deficits (Lezak, Howieson, Bigler, & Tranel, 2012; Wester, Leenders, Egger, & Kessels, 2013). Still, the RBMT was able to discriminate moderate from severe memory impairments, as evident by the significant difference between KS and CI patients on all subtests. Comparing ALC and CI patients using the CVLT showed that rate of forgetting was significantly lower for ALC patients, and ALC patients also performed significantly better on short-term and long-term free recall. This pattern of 'rapid forgetting' is similar to what was found in the KS group, that is, decay from immediate to delayed testing. This result seems in contrast with previous studies on forgetting in KS patients indicating impaired acquisition, yet normal forgetting rates (Huppert & Kopelman, 1989; Martone, Butters, & Trauner, 1986). However, CVLT forgetting rate is assessed using free-recall tests, which are more susceptible for motivational factors or retrieval deficits than cued-recall or recognition tests. Indeed, the delayed cued recall and recognition trials of the CVLT enhance the memory performance in KS patients, albeit that the performance is lower than the ALC and CI group. The discrepancy between free and cued-recall/recognition is also evident in the CI group, who obtain even unimpaired scores on the cued recall and recognition trial.

A combination of two discriminant functions makes it possible to discriminate significantly between the three patient groups. Examining the relative contribution of the subtests to the first discriminant function also highlights that measures of free and cued recall of the CVLT are better at discriminating than recognition performance. With respect to the second discriminant function, immediate and delayed testing of a newspaper story (Story Recall) in the RBMT added to the discrimination of the groups. This subtest differs from the other subtests of the RBMT in that a large amount of information is presented in a free-recall format, in contrast to all other subtests that rely on recognition and/or have a limited information load. It also differs from the CVLT in that the information of the RBMT Story Recall is largely contextual in nature, in contrast to the single words of the CVLT. Although CVLT items can be semantically categorized, the contextual aspect of the RBMT Story can be argued to have a stronger episodic component which determines the impairment in KS patients (cf. Kessels & Kopelman, 2012). In addition, prose recall relies on detailed information processing which requires more motivation and attention than other RBMT and CVLT subtests. Indeed, lowered motivation has previously been found to hamper the performance on prose recall tests in KS patients (Davidoff et al., 1984). The CI and AL groups did not differ on the RBMT Story Recall subtest, in agreement with previous studies (e.g. Uecker mann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003).

ROC analyses showed that the total standardized profile score of the RBMT and the total score of the CVLT could significantly discriminate KS from CI patients, but were not capable of distinguishing CI from ALC patients. This insensitivity of the RBMT for more subtle memory impairments has led to a recent revision of this test resulting in the RBMT-3 to overcome this insensitivity (Wilson et al. 2008). Indeed, the Global Memory Index of this revised RBMT-3 – comparable to the RBMT total standard profile score – was able to discriminate chronic alcoholics with and without cognitive impairments (Wester, Van Herten, Egger, & Kessels, 2013). In addition, the CVLT total score only reflects the acquisition of new information, but does not include the delayed (cued) tests, which, as argued above, are most sensitive to alcohol-related memory deficits.

So far, only one study examined the discriminating capability of the RBMT directly comparing two patient groups (Glass, 1998). That retrospective analysis of RBMT subtest scores in a clinical sample of 74 dementia patients demonstrated significant differences between patients with vascular dementia and patients with nonvascular dementia on four of the RBMT subtests, i.e. Appointment, Route Recall, Story Recall and Message. Apart from the Story Recall subtest, this does not overlap with the subtests identified in the present discriminant analysis. However, the type of patients under investigation differs, i.e. two groups of dementia patients (who may both be severely cognitively impaired, see also Glass, 1998) compared to severely amnesic KS patients and milder cognitively impaired alcoholics in the present study.

A limited number of studies compared the RBMT to more ‘standard’ or ‘traditional’ memory tests. Pérez and Godoy (1998) found that the RBMT was as robust as the Wechsler Memory Scale-Revised (WMS-R) in the ability to discriminate patients with Alzheimer’s disease or epilepsy from older controls with or without memory complaints. A similar observation was made by Koltai, Bowler and Shore (1996) in patients exposed to neurotoxics, showing similar diagnostic accuracy for the RBMT and the WMS-R. Although the RBMT stimuli have been developed to be more ‘real life’ than those of traditional tests like the WMS-R, their actual administration procedures and the test designs are highly similar. That is, both memory batteries consist of short subtests, and include prose and picture recall tasks. To our knowledge, only one study exists in which both the RBMT and the CVLT were administered simultaneously. However, that study (Quemada et al., 2003) focused on the rehabilitation outcome of a small sample of traumatic brain injury patients and did not directly compare the tests’ diagnostic accuracy.

To conclude, a combination of the RBMT subtests and the CVLT indices can be used to discriminate KS patients from alcoholic patients without cognitive impairment or with non-Korsakoff cognitive deficits. To distinguish cognitively

CHAPTER 4

impaired and unimpaired alcoholics who do not fulfil the criteria for KS, the discrepancy between immediate and delayed CVLT trials (i.e. rate of forgetting) as well as a comparison between free and cued recall testing on the CVLT appears the most informative. The RBMT could not significantly discriminate cognitively impaired from unimpaired alcoholics. Future studies should examine whether the recently developed RBMT-3 overcomes this insensitivity.

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A COMPARISON BETWEEN THE RBMT AND THE CVLT

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5

CHAPTER

Psychometric properties of the RBMT-3

In preparation:

Lazeron-Savu, E.P., Wester, A.J., Bouman, Z., Egger, J.I.M., & Kessels, R.P.C.
Psychometric properties of the Dutch version of the Rivermead Behavioural
Memory Test - third edition.



Abstract

The latest edition of the Rivermead Behavioural Memory Test (RBMT-3), a test battery assessing memory abilities needed for the performance of daily-life activities, has undergone a number of changes to improve the quality of the measurements and the applicability of the test. This study examines the reliability and validity of the Dutch version of the RBMT-3 in 141 healthy Dutch-speaking adults aged between 18 and 77 years. Nineteen participants completed both parallel versions after a brief interval. Cronbach's α (0.68) showed the test to have fairly good reliability, while a principal component analysis indicated that the test is homogeneous, with Bland-Altman plots and intraclass correlation analyses supporting a good content and construct validity. Age and verbal intelligence, but not sex and educational level, showed an effect on performance. Normative data for the Dutch population were computed. Based on the results it is concluded that the Dutch adaptation of the RBMT-3 is a reliable and valid tool to monitor changes in memory functions.

Introduction

Memory problems are one of the most common cognitive problems. They occur in many neurological disorders, such as dementia, delirium and brain trauma, but also in other conditions, such as depression and thyroid problems (Lezak, 2004). A wide range of tests is available to assess memory (dys)function, with many gauging specific aspects of memory. Examples are the N-back test that evaluates different domains of working memory (Kirchner, 1958) and Rey's Auditory Verbal Learning Test that examines various aspects of long-term verbal memory (Van der Elst, 2006). Also extensive test batteries exist that assess a continuum of memory functions like the Wechsler Memory Scale (WMS; Lezak, 2004). Only a few test batteries examine disturbances in memory functions in everyday tasks, of which the WMS is one. The Rivermead Behavioural Memory Test (RBMT) was specifically developed to evaluate impairments in 'everyday' memory (Wilson, Cockburn, Baddeley, & Hiorns, 1985). In the Netherlands, Van Balen and Groot Zwaaftink translated and researched the RBMT, releasing the Dutch version in 1987 (Van Balen & Groot Zwaaftink, 1987).

The RBMT consists of twelve subtests: first and second names, belongings, appointments, picture recognition, immediate and delayed story recall, face recognition, immediate and delayed route recall, immediate and delayed messages recall, and orientation and date recall. On the basis of the performance outcomes, screening and profile scores can be calculated. Originally, four parallel versions were developed to allow changes over time to be monitored while ruling out learning effects. Several adaptations of the test followed, such as the RBMT-C that was specifically designed to assess children in the ages of 5-11 years (Aldrich & Wilson, 1991). In 1999 two of the original test versions were combined into the RBMT-E. Also, more items were added, allowing milder memory problems to also be identified (Wilson, Clare, Baddeley, Cockburn, Watson, & Tate, 1999). Finally, a revised version appeared in 2003, named the RBMT-II, which took into account multicultural aspects, i.e. non-Caucasian faces in the Face Recognition Test (Wilson, Cockburn, & Baddeley, 2003).

The results of the various studies conducted worldwide showed that the RBMT is a reliable and valid tool to assess verbal and visuospatial episodic (long-term) memory (Efklides et al., 2002; Yassuda et al., 2010). Further research indicated that the RBMT is a good predictor of memory problems in everyday life and thus has ecological validity (Cockburn & Smith, 1989; Davis, Cockburn, Wade, & Smith, 1995; Malec, Zweber, & DePompolo, 1990; Fraser, Glass, & Leatham, 1999; Van der Feen et al., 1990). The normative study of the original Dutch version produced no significant effects for age and level of education, neither for the test nor its subtests (Van Balen & Groot Zwaaftink, 1987).

In 2008 Wilson and colleagues published the latest edition of their test, the RBMT-3, with two parallel versions, each with 14 subtests whose complexity was adjusted to a level that was believed to capture present-day life better. Also, the stories were modernized and a new subtest, entitled Novel Task, was added. This additional subtest assesses working memory capacity, i.e. the ability to learn a new skill, both in an immediate and a delayed condition. The RBMT-3 accordingly affords a more extensive assessment of human memory functions.

We recently evaluated the ceiling and floor effects of the Dutch translation of the RBMT-3 in patients and healthy participants (see Chapter 6) and found the revised test to have substantially improved on both parameters compared to its predecessor, as well as showing better specificity and sensitivity. Examining the validity of the RBMT-3 in patients with alcohol-related cognitive disorders, (see Chapter 7) we again found good sensitivity and adequate specificity, as well as evidence that the test correctly quantified and qualified everyday memory problems in this population. In the current study we examine the psychometric properties of the Dutch version of the RBMT-3 in a sample of age-representative healthy Dutch volunteers.

Wilson et al. (2008) examined their revised test in a large sample that was representative of the demographics of the United Kingdom, but omitted to evaluate the effects of age and verbal intelligence on test performance. Especially age and verbal IQ are thought to be vital for a correct interpretation of the test results, even more so because the RBMT-3 is supposedly more sensitive but, as a result, also more difficult than the earlier versions (Wester et al., 2013a,b). Assessing a large sample of healthy adults and patients with Alzheimer disease ($n = 233$; age range 20-76 yrs) with the Greek version of the RBMT in 2002, Efklides et al. found that age correlated negatively ($r = -0.44$) with performance. The normative study of the Dutch version, in contrast, did not uncover a significant effect of age in healthy adults ($n = 213$; age < 70 yrs; Van Balen & Groot Zwaaftink, 1987), while verbal intelligence was found to correlate with test scores to a small degree ($r = 0.38$) in 70-95-year-old healthy English volunteers (Cockburn & Smith, 1989). Given its greater sensitivity and complexity, we expect that age and verbal intelligence will have a greater effect on RBMT-3 performance.

To calculate the reliability coefficients for the two parallel versions of the RBMT-3, Wilson et al. (2008) opted for alternate-form reliability and obtained values between 0.26 and 0.70 for the subtests in their standardization sample. However, this type of reliability estimate does not necessarily imply perfect agreement. For example, a systematic change in the results on one subtest does affect the agreement but not the alternate-forms reliability coefficient. The change rather indicates a systematic difference between the mean of the two

test occasions and the mean of the subtests (Bland & Altman, 1986; Holmefur, Aarts, Hoare, Krumlinde-Sundholm, 2009). Lexell and Downham (2005) described such systematic changes or differences as nonrandom changes in the mean values of two separate assessments, i.e. changes that arise when an examinee performs better or worse the second time he or she completes the test, which might be due to a change in motivation, a learning effect or fatigue. Before one can conclude that the test measures what it is intended to measure, it is crucial that these factors are controlled for. Wilson and colleagues (2008) reported that a memory index factor could be extracted on which the other subtests have a high load. We expect to be able to do the same for the Dutch version.

With the present study we aim to determine the internal consistency and reliability of the Dutch version of the RBMT-3 and to look for effects of age, verbal intelligence and level of education on performance scores to test its validity.

Method

Participants

A total of 141 healthy adult participants (age range 18-77 years) were recruited from an ongoing investigation at the Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. Initially, most volunteers were staff working at the institute's Korsakov Clinic and because the majority were relatively young women (female professional caregivers) their male partners or family members (brothers or fathers) were also invited to participate. Additionally, members of the institute's museum committee were enlisted to obtain a subsample of relatively older male participants, making the total sample more age-representative of the general Dutch population. None of the participants had any known neurological or psychiatric history and none were taking prescribed medication at the time of testing. All investigations and assessments were conducted by experienced psychologists of the Korsakov Clinic trained in test administration.

Seven educational levels were initially distinguished, with 1 reflecting little or no formal schooling (below elementary-school level) and 7 corresponding with one or more academic degrees; Verhage, 1964). Because not all categories had a sufficiently large number of subjects, we decided to use a dichotomous variable: high-school or less (Verhage categories 1-5) or more than high school (categories 6-7).

Material

The participants completed all 14 subtests of the RBMT-3 (Figure 1) in Dutch translation and performance was scored according to the instructions in the

manual (Wilson et al, 2008). The subtests gauge everyday memory in terms of: first and second names, belongings, appointments, picture recognition, story (immediate and delayed recall), face recognition, route (immediate and delayed recall), messages (immediate and delayed recall), orientation and date, and novel task (immediate and delayed recall). Nineteen participants also completed the second, parallel version of the RBMT-3 after approximately 3.5 months (range: 1 day to 5 months).

Besides the RBMT-3, participants took the NLV, the national (Dutch) adult reading test (Schmand, Lindeboom, & Van Harskamp, 1992) that assesses level of verbal intelligence. Participants are asked to read aloud a series of words that have an irregular pronunciation, with the number of correctly pronounced words being taken to reliably reflect their level of verbal IQ.

Statistical Analysis

For our statistical analyses we used the raw scores as well as the raw scores transformed into z-scores, giving every subtest score the same weight to thus facilitate the comparison and interpretation of performance measures (Gregory, 2011). To obtain an index score, i.e. the RBMT-3 Memory Index (MI), all the z-scores a participant attained for each of the subtests were added together and divided by the number of subtests ($n = 14$). Wilson et al. (2008) calculated scaled scores from the raw scores and a General Memory Index (GMI) for the overall score. Although we used the raw scores to compute the MI for our sample, it is comparable with the GMI in that both are computed by summing the subtest scores.

The internal consistency of the RBMT-3 was investigated using the subtest raw scores. Cronbach's alpha coefficient was computed to determine the scale's reliability, while reliability at the subtest level for the two versions was determined by intraclass correlations (ICC; model 2, 1 according to Shrout and Fleiss, 1979). Systematic performance differences for the two test sessions were investigated using Bland-Altman plots, with the differences between versions 1 and 2 being plotted against their means and the limits of agreement being calculated as the mean of the between-version differences ± 2 standard deviations (SDs) of these differences. The standard error of the mean and the 95% confidence interval (CI) for the mean difference between versions were also calculated. When the 95% CI does not include zero, this indicates a systematic change in the mean, possibly due to a learning effect or another confounding factor. Another index of agreement is the mean of the bias, which for a perfect agreement must be zero. The line of equality is also useful for detecting a systematic difference: if the line of equality does not reach the 95% CI of the mean difference, the difference is systematic and statistically significant

(Bland & Altman, 1986, Lexell, & Downham, 2005). The test's construct validity was explored by principal component analysis (PCA).

A linear regression analysis was used to analyse whether age, education and verbal intelligence had affected RBMT-3 performance. To see whether relationships between age and MI were moderated by verbal IQ or educational level we evaluated the corresponding two-way interactions in the linear regression analyses with age and verbal IQ, and age and education as the independent variables, and performance scores on one of the parallel versions as the dependent variable. Sex-dependent effects were examined by means of analysis of variance (ANOVA). Regression cut-off scores were determined using linear regression analyses, with MI as the dependent variable and age and verbal IQ as predictors (van den Berg et al., 2009). The regression-based norms allow controlling for a number of demographic predictor variables. This analysis also treats age as a continuous variable (Smerbeck et al., 2012).

Results

Descriptive data (means and SDs of age, verbal intelligence and educational level) are shown in Table 1. Table 2 presents the means and standard deviations of the scores on the 14 subtests for both versions of the RBMT-3. Figure 1 shows the correlations between the Memory Index and the General Memory Index for the Dutch participants, as well as their means and standard deviations.

Table 1 Means and standard deviations of age, verbal intelligence and educational level (dichotomy) of the participants.

	Age (n = 141)	Verbal IQ (n = 127)	Educational level (n = 141)
Mean	46.74	99.81	5.41
Standard deviation	13.02	11.56	0.91

We obtained a Cronbach's alpha of 0.68 for the 14 RBMT-3 subtests, reflecting a fairly good reliability. Table 3 shows what the coefficient α would be in each case if the subtest was deleted and it also shows the correlations of each subtest with the total test score and the loading values of the subtests on the Memory Index. The exclusion of four subtests increased the value of α : Belongings (0.681), Appointments (0.682), Picture Recognition (0.686) and Novel Task-immediate

Table 2 The means (M) and standard deviations (SD) of the performance on the 14 subtests for the two parallel versions, in the Dutch sample.

RBMT-3 subtest scores	Version 1 (n =141) M (SD)	Version 2 (n =19) M (SD)
First and Second Names	6.07 (2.00)	5.89 (2.02)
Belongings	6.99 (1.35)	7.47 (1.30)
Appointments	3.28 (0.887)	3.21 (0.91)
Picture Recognition	14.66 (0.705)	14.68 (0.74)
Story_IR	7.83 (3.10)	8.95 (3.40)
Story_DR	6.66 (3.13)	7.18 (3.25)
Face Recognition	13.31 (1.50)	13.42 (1.07)
Route_IR	11.52 (2.15)	12.63 (1.11)
Route_DR	11.76 (2.13)	12.26 (1.55)
Messages_IR	5.74 (0.64)	5.89 (0.45)
Messages_DR	5.66 (0.79)	5.89 (1.55)
Orientation and Date	12.83 (1.13)	13.32 (0.88)
Novel Task_IR	38.63 (9.13)	48.58 (0.88)
Novel Task_DR	14.69 (3.11)	15.95 (2.59)

recall (0.726). The subtests that contributed to the internal consistency of the scale had correlations higher than 0.5 and subtests with a small contribution correlations around 0.1. As to our PCA exploring construct validity, the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.682, and Bartlett's test of sphericity was significant, $\chi^2(91) = 617.314$ $p < 0.001$, reflecting high sampling adequacy, which indicates that the 14 subtests together constitute a one-dimensional scale: five components have an eigenvalue above 1 but there is an evident distance (Fig. 2) between the first component and the other components, with the first factor explaining 26% of the total variance. All subtests had positive correlations with the first component, wherein the variable Route-immediate recall had the highest consistency (component load 0.734), while the lowest consistencies were noted for Picture Recognition (0.16), Appointments (0.121) and Belongings (0.178).

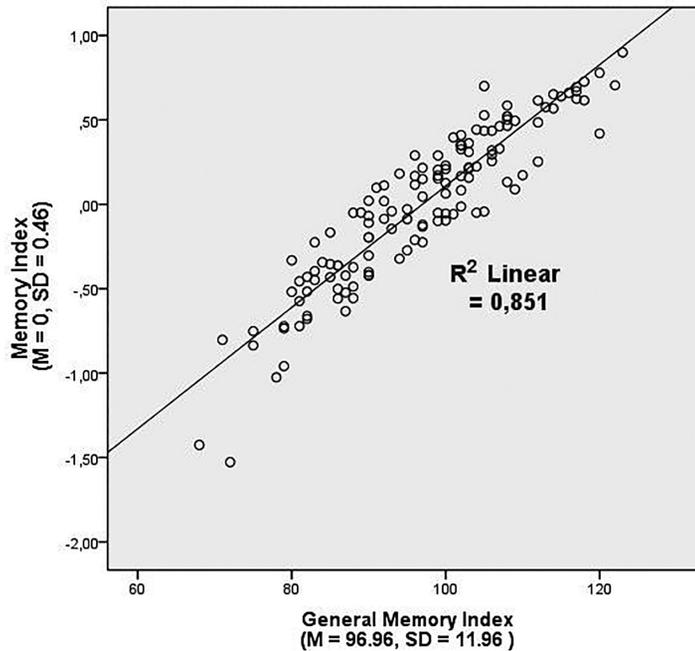


Figure 1 The correlations between the Memory Index and the General Memory Index and the means and standard deviations of the two indices

Table 4 shows indices of change in the means between the two test versions, the Bland-Altman limits of agreement and the stability and equivalence coefficients (Intraclass Correlations; ICC). The subtests that showed no systematic changes are Messages (0), Appointments, Picture Recognition, Face Recognition (0.16) and Orientation and Date (-0.16). Systematic changes were obtained for the Story-immediate and delayed recall and Novel Task-immediate recall subtests. The mean differences for these subtests are far from zero and as zero is not included in the 95% CI, the change is significant. There were other subtests that also had a mean difference far from zero but their 95% CI included zero, rendering the change not significant. Our analysis of the alternate-forms subtest reliabilities revealed ICC values of 0.725, signifying moderate reliability. The high coefficients computed for the subtests Story-immediate and delayed recall ($r = 0.748$ and $r = 0.604$, respectively), Orientation and Date ($r = 0.485$) and Novel Task-immediate recall ($r = 0.512$) were all significant ($p < 0.05$), suggesting good stability and equivalence.

Table 3 Correlations of each subtest with RMBT-3 total score, the values of what coefficient α would be if the subtest was deleted and the loading values of the subtests on the Memory Index.

RMBT-3 subtests	Corrected Subtest Total Correlation	Cronbach's alpha if Subtest Deleted	Subtest loadings on the index factor
First and Second Names	0.217	0.674	0.323
Belongings	0.118	0.681	0.178
Appointments	0.092	0.682	0.121
Picture Recognition	-0.009	0.686	0.016
Story_IR	0.594	0.621	0.725
Story_DR	0.576	0.623	0.719
Face Recognition	0.181	0.677	0.211
Route_IR	0.526	0.644	0.734
Route_DR	0.471	0.649	0.678
Messages_IR	0.294	0.677	0.431
Messages_DR	0.225	0.678	0.358
Orientation and Date	0.325	0.671	0.460
Novel Task_IR	0.566	0.726	0.680
Novel Task_DR	0.636	0.614	0.646

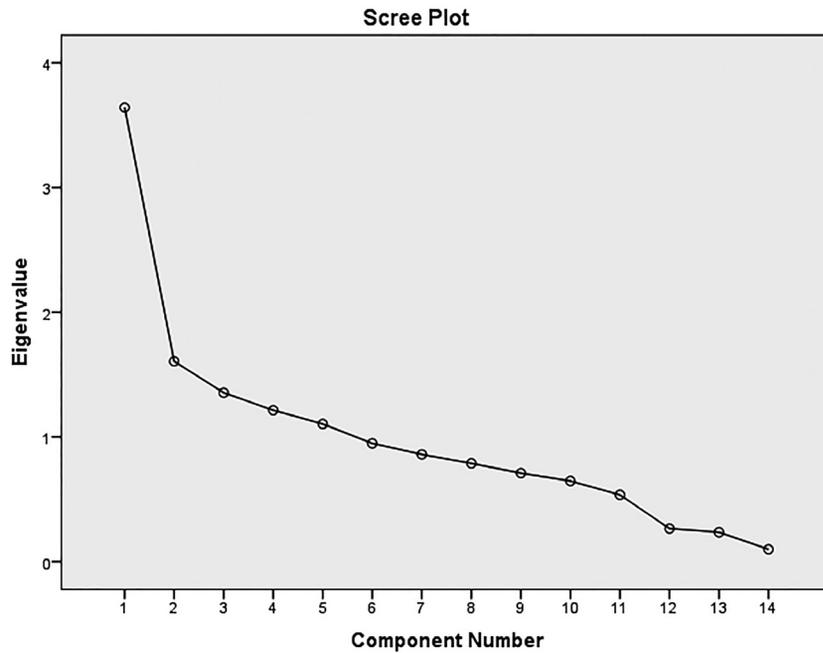


Figure 2 The scree plot of the data that graphs the eigenvalue of the extracted factors against the factor number

Visual inspection of the raw scores, ages and verbal IQs showed a normal distribution, and the ANOVA did not yield a main effect of sex on the RBMT-3 Memory Index, $F(1,139) = 0.444$, $p > 0.5$. The independent linear regression analysis showed that age and verbal IQ had a significant effect on MI: $F(1,123) = 25.234$, $p < 0.001$. Age and verbal IQ predicted the results on the index score although prediction power was moderate: 38% of the variance in MI was predicted by age ($R^2 = 0.381$, Age $b^* = -0.542$, $t = -7.124$, $p < 0.001$, 95% CI [-0.025, -0.014]), with verbal IQ ($R^2 = 0.381$, $b^* = 0.290$, $t = -3.658$, $p < 0.001$, 95% CI [0.005, 0.018]) having a significant, moderately strong correlation with MI. Education levels had no effect on MI ($R^2 = 0.381$, $b^* = 0.014$, $t = 0.164$, $p > 0.5$, 95% CI [-0.142, 0.168]). Linear regression analyses revealed that the interactions between age and verbal intelligence ($b^* = 0.107$, $p = 0.136$) and age and education ($b^* = 0.245$, $p = 0.311$) had no significant effect on MI. Verbal IQ and education had no moderating effect on age and together the factors were not related to MI. All the regression analyses met the assumption criteria.

Table 4 Change indices for the mean performance scores on the two RBMT-3 parallel versions with stability and equivalence coefficients

RBMT-3 subtests	M	SD	SE	95% CI	95% CI	l.of a. +	l.of a. -	ICC
First and Second Names	1.16	3.18	0.73	2.62	-0.30	7.39	-5.08	-0.13
Belongings	-0.37	1.67	0.38	0.44	-1.17	2.91	-3.65	0.10
Appointments	0.16	1.12	0.26	0.69	-0.38	2.35	-2.03	0.18
Picture Recognition	0.16	0.60	0.14	0.45	-0.13	1.34	-1.02	0.60
Story_IR	-2.18	2.35	0.53	-1.05	-3.31	2.41	-6.78	0.74
Story_DR	-1.5	2.45	0.59	-0.32	-2.68	3.31	-3.58	0.67
Face Recognition	0.16	1.46	0.34	0.86	-0.55	3.02	-2.70	0.12
Route_IR	-0.95	2.17	0.49	0.09	-1.99	3.31	-5.20	0.18
Route_DR	-0.79	2.88	0.66	0.59	-2.17	4.85	-6.43	0.03
Messages_IR	0	0.67	0.15	0.32	-0.32	1.31	-1.30	-0.05
Messages_DR	0.21	0.92	0.21	0.23	-0.65	1.58	-2.00	-0.10
Orientation and Date	-0.16	0.83	0.19	0.24	-0.56	1.48	-1.79	0.48
Novel Task_IR	11.84	9.92	2.28	-7.06	-16.62	7.60	-31.29	0.51
Novel Task_DR	-1.31	4.38	1.00	0.79	-3.42	7.28	-9.91	-0.01

Notes: M = mean difference between two test occasions; SD = standard deviation of the difference between two test occasions; SE = standard error of mean; 95% CI = confidence interval of mean; l.of a. = limits of agreement

Discussion

To determine the psychometric properties of the Dutch version of the RBMT-3, in the current study we evaluated the performance scores on all its 14 subtests in an age-representative sample of 141 healthy adults. The Cronbach's α values we obtained showed the test to have moderate reliability. Exclusion of four subtests, i.e. Belongings, Appointments, Picture Recognition and Novel Task-immediate recall, increased the reliability coefficient. The Picture Recognition, Appointments, Belongings and Face Recognition subtests were not as closely associated with

the total score as the other subtests were. We found the RBMT-3 to have solid construct validity and, using a principal components analysis, were able to subtract one general factor, i.e. the Memory Index (MI), with all subtests having a positive loading on this general factor. For 11 of the 14 subtests the loading on MI was moderate to high, but loadings were low for the Belongings, Appointments and Picture Recognition subtests. The combined results suggest that the RBMT-3 subtests measure what they are proposed to measure to a moderate degree. Overall, our findings are consistent with those of Wilson et al. (2008) reported in the UK manual. However, their reliability coefficients were higher, which difference may be attributable to our smaller sample size.

Also they concluded that the reliability coefficients of the RBMT-3 were compromised by the restricted dispersion of the scores in healthy participants given that most can perform the subtests well. Indeed, Wilson et al. (2008) found better reliability when they evaluated the RBMT-3 in a patient group. Our reliability coefficients for the Dutch version accordingly also need the same verification in patient samples. The finding that reliability varies across subtests is in agreement with previous findings on the original RBMT. For example, examining the validity and reliability of the RBMT in a Brazilian population, Yassuda et al. (2010) attributed the test's moderate reliability to the high variability of its subtests. The subtests all measure different aspects of memory, i.e. both episodic and prospective memory capacity in verbal, visual, spatial as well as time dimensions, using different test paradigms such as recognition and free recall, which factors all contribute to the variation in subtests scores.

As mentioned above, the results we obtained show that three subtests gauge other concepts than the other subtests do. Wilson et al. (2008) also attained lower loadings on the general factor for the Picture Recognition and Belongings subtests. Not surprisingly, Efklides et al. (2002) recorded that the RBMT Belongings, Appointments and Picture Recognition subtests had a high loading on a factor that taps prospective episodic memory capacity. Prospective memory involves memory functions that are necessary to execute a planned action or intention at the appropriate time, a capacity we use in the performance of everyday activities that is quite distinguishable from other types of memory as it focuses on intended future events and not on acquired knowledge and skills (McDaniel & Einstein, 2007). Given these various points, it seems opportune for a short test battery to be constructed that specifically gauges prospective memory, which would then consist of the Belongings, Appointments, Picture and Face recognition subtests. As Smith, Sala, Logie, and Maylor (2000) reported that it are precisely these prospective memory problems that are the first deficits to be reported by caregivers of patients with Alzheimer disease, the proposed test could then be applied in clinical practice to objectively screen for

and monitor these specific deficiencies in patients suspected of or diagnosed with Alzheimer's dementia.

The Bland-Altman analyses we computed for the performance scores on the two RBMT-3 versions revealed that 11 subtests did not show a statistically significant systematic change, implying the absence of a bias between the two versions. The immediate recall condition of the Messages subtest showed no change whatsoever. This lack of systematic changes in so many of the subtests supports the good content validity of the test, confirming that its subtests indeed measure a common construct (Nunnally & Bernstein, 1994). In contrast, the analyses for the three remaining subtests, i.e. Story-immediate and delayed recall, and Novel task-immediate recall did reveal significant differences between the two parallel versions. It is likely that these changes arose from a change in strategy due to a learning effect; having completed the first version, the participants had inferred that for successful performance of these tests attention to detail was essential, knowledge that they later utilized for the completion of the second version. The change cannot be attributed to a change in behaviour or to fatigue as other subtests would then have shown similar changes, while it has never been reported that these particular subtests are more sensitive to these factors than the other subtests. The fact that our participants completed the two test versions within a relatively, sometimes even extremely short period (after 1 day; mean 3.5 months) provides additional support for our learning effect hypothesis. Tests tend not to be repeated within such a short timeframe in clinical practice,

The systematic difference between the two versions of the Novel Task may be due to the faculty that is being tested, i.e. the ability to learn a new skill. Once a task has been mastered, it will remain an acquired skill, at least for some time. As the subtest gauges procedural memory, and given the short test-retest interval, this would then explain the performance changes. The recorded bias change can then be interpreted as a priming effect, which interpretation is underlined by an other study (see Chapter 7) in which healthy participants also attained close-to-perfect scores in the delayed recall condition of this subtest.

Schmidt and Le (2007) proposed that since the ICCs for stability and equivalence reliability take into account all three types of error measurements, i.e. random response, transient and specific factor errors, the coefficient generates lower values than split-half or alternate-form reliabilities for instance. In our study the most stable and equivalent subtest was Story-immediate recall, followed by Story-delayed recall and Picture Recognition. The less stable and less equivalent-over-time subtests were Names, Message-immediate recall, Message-delayed recall and Novel task-delayed recall. That the immediate and delayed recall conditions of the Story subtest show a discrepancy between their

stability and equivalence coefficients and their Bland-Altman plots is then plausible as the correlation simply assesses the extent of linearity between two measurements, while the Bland-Altman analyses represent the total agreement between the two test versions (Bland & Altman, 1986).

As to the validity of the RBMT-3 Dutch version in terms of age, sex and education-related effects, we found no effect of sex. Our findings correspond with those in studies evaluating the RBMT-I, which likewise reported no gender-related associations (Cockburn & Smith, 1989; Efklides et al., 2002; Van Balen et al., 1996; Wilson et al., 1985). Given that human memory performance declines with increasing age, and thus as predicted, we did find strong effects of age, with its contribution to the scores being high and its relationship negative, that is, the younger the participant, the better the results were. Age-related cognitive decline is thus effectively reflected by this latest version of the RBMT. The different studies of the RBMT reported mixed findings on the effects of age (Van Balen et al., 1996) and, Wilson et al. (2008) reported an expected age effect for the RBMT-3. Our results support these earlier age-dependent findings. The present study is the first to examine the influence of IQ on the RBMT -3 and, also confirming our hypothesis, we found verbal IQ to have a significant, moderate effect on the test scores.

It needs to be mentioned that the recruitment procedure we adopted in this study resulted in demographic homogeneity. First, all participants originated from one region of the country; whether results vary significantly depending on the region thus warrants verification. Second, good normative data require a broad range of educational levels but the spread in our sample was limited, with participants in the higher education bracket being overrepresented. Finally, the number of participants who completed both versions of the RBMT-3 is small ($n = 19$). Accordingly, future research should include more participants in a wider cross-section of educational backgrounds to increase the reliability of our current findings.

In conclusion, we found the Dutch version of the RBMT-3 to have moderate reliability with most (10 of its 14) subtests measuring the same concept. Four subtests appear to measure other concepts. Intraclass correlation analysis of its two parallel versions supported good content and construct validity. Test scores showed effects of age and verbal intelligence. Future research should expand the sample of healthy participants in order to compute reliable normative data for use in clinical practice. Also the test's convergent validity is to be researched, for example using other memory test batteries such as the fourth edition of the Wechsler Memory Scale (WMS-IV).

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6

CHAPTER

Ceiling and floor effects on the RBMT and the RBMT-3

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Abstract

Objective: The Rivermead Behavioural Memory Test (RBMT) is a widely used measure of everyday memory performance. In the most recent revision of this test (RBMT-3) some important changes have been made compared to the RBMT. This study examines whether this revision has improved the quality of the clinical classifications using this test, as well as the frequency of floor and ceiling performances that were prominent on some subtests of the RBMT, using a heterogeneous study sample.

Methods: 25 healthy adults and 25 patients with alcohol-related memory impairment, (including 15 Korsakoff patients) were examined using both the RBMT and the RBMT-3. The number of perfect scores and floor performances were scored and compared, as well as the percentage of individuals classified as impaired (< 5th percentile).

Results: Administration of the RBMT-3 results in less participants performing at or near individual subtest's ceiling, and resulted in less floor performances. Moreover, the RBMT-3 misclassifies less healthy participants as impaired than the RBMT.

Conclusions: The RBMT-3 is a substantial improvement over the original RBMT, as it reduces the problem of ceiling and floor performances and the number of misclassifications. However, more research is needed on the ecological validity of the RBMT-3.

Introduction

Memory impairments are among the key deficits in a variety of neuropsychiatric or neurologic disorders or diseases, such as Alzheimer's disease, schizophrenia, Korsakoff's syndrome, stroke or traumatic brain injury. A wide range of neuropsychological tests is available for the assessment of memory. Typically, these tests measure memory for word lists, digit sequences, patterns or pictures (for an overview, see Lezak et al. 2012). Many of these widely available memory tests have, however, been criticized as they do not resemble everyday memory tasks and may as a result have limited predictive value for everyday functioning, often referred to as ecological validity (Spooner and Pacahna 2006). To overcome this shortcoming, Wilson et al. (1985, 1989) were the first to develop an ecologically valid memory test battery resembling everyday tasks, the Rivermead Behavioural Memory Test (RBMT), with the aim to measure daily memory function in relation to cognitive rehabilitation. The RBMT consists of a number of subtests, covering episodic memory, prospective memory and orientation, and has four parallel versions for monitoring of changes over time. The RBMT has been widely used over the years in, for example, patients with MCI or Alzheimer's disease (Yassuda et al. 2010), vascular dementia (Glass, 1998), schizophrenia (Guaiana et al. 2004) and Korsakoff's amnesia (Oudman et al. 2012). Also, the RBMT has been translated into many languages from the original UK version, including Japanese (Mori and Sugimura, 2007), Dutch (Van Balen et al. 1996), Portugese (Yassuda et al. 2010) and Turkish (Küçükdeveci et al. 2008).

However, several subtests of the RBMT consist of only a relatively low number of stimuli (e.g., five photographs of faces or ten line drawings) and/or use a recognition memory format which makes these subtests relatively easy. As a result, the RBMT may be less sensitive for milder forms of memory impairment (Wilson et al. 1985). The Extended Version of the RBMT (RBMT-E) has been developed (Wilson et al. 1998) to be more sensitive for mild memory deficits by increasing the number of stimuli of some subtests and making them more complex. Indeed, direct comparison of the RBMT and the RBMT-E demonstrated that patients who performed in the normal range on the RBMT showed deficits on the RBMT-E (Wills et al. 2000). The RBMT-E, however, has to our knowledge not been translated into other languages and as a result did not gain popularity outside the Anglo-Saxon world.

Recently, Wilson and colleagues have published the third edition of the RBMT (RBMT-3). In this revised version, stimuli have been updated, and the number of trials per subtest was substantially increased, in line with the previously published RBMT-E. Moreover, a new subtest was introduced measuring procedural learning, the Novel Task, in which a puzzle has to be

solved in a fixed order according to a modeled performance (Wilson et al. 2008). Also, inclusion of a newly developed Implicit Memory Test (IMT) into the revised RBMT was considered (Sopena et al. 2005). However, while implicit memory assessment would have been a valuable addition to existing memory batteries, performance on the IMT may lack reliability and may be confounded by explicit memory function (Kessels et al. 2010). Table 1 shows brief descriptions of the subtests of both the RBMT and the RBMT-3, as well as the changes that were made in the revised RBMT-3 compared to the RBMT.

The revisions made in the RBMT-3 may have increased the applicability of this memory battery in clinical practice, compared to the RBMT. That is, even some severely amnesic patients demonstrated a ceiling performance on subtests of the RBMT (Wester 2007). Increasing the number of stimuli of some subtests of the RBMT-3 may have overcome this limitation. On the other hand, increasing the complexity of a cognitive test and increasing the amount of to-be-learned information may also result in less optimal performance in patients, for example, due to fatigue or lack of motivation, limiting the test's feasibility in clinical practice. Furthermore, one could argue that a too difficult test may even enhance the occurrence of floor effects in participants with memory deficits. In the present study, we set out to examine whether administration of the RBMT-3 in patients with alcohol-related memory deficits and in healthy adults results in less ceiling and floor performance on all individual subtests compared to the RBMT at subtest level. Also, the revision may have improved the diagnostic accuracy of the test, which can be examined by comparing individuals with memory impairments due to chronic alcohol abuse and healthy volunteers, and applying clinically accepted cut-off values. Using this approach the number of individuals classified as being impaired on each subtest can be determined for both tests and both groups (healthy vs. memory-impaired).

Thus, the aim of the present study is twofold: 1) we will investigate and compare the occurrence of floor and ceiling effects on the individual subtests of the RBMT and RBMT-3 in a heterogeneous sample consisting of healthy participants and cognitively impaired patients; 2) we will examine the number of misclassifications for each version of the test, that is, healthy participants being classified as having a memory impairment and memory-impaired individuals as having no deficit. We purposely selected a heterogeneous study sample consisting of individuals without any evidence of memory impairment (healthy volunteers) and patients with mild cognitive deficits due to alcohol-abuse disorders, as well as patients with severe amnesia due to Korsakoff's syndrome.

Table 1 RBMT and RBMT-3 subtests, the memory aspect they assess and the changes made in the revised version

Subtest	Description	Changes made in revised RBMT-3
Names	Remember first and last name of photograph	Updated material
Belonging	Two personal belongings are hidden, and the participant has to ask for them at the end of the test	No changes
Appointments	An alarm clock is set, if it sounds the participant has to ask two questions	Minor changes, i.e. two questions have to be asked instead of one
Pictures	Recognition memory test of 15 line drawings, later presented with distracter items	Increased number of items, updated stimuli
Story	A short newspaper story is read aloud, the examiner has to recall as many details, both immediately after presentation and after a delay	New, revised stories of similar complexity
Faces	Recognition memory of 15 photographs of faces, later presented with distracter items	Updated material (inclusion of non-Caucasians), increased number of stimuli
Route	A short route in the examination room has to be retraced, immediately and after a delay	Increased number of route sections, option to retrace the route on a paper sheet deleted
Messages	Examiner has to pick up envelope that was placed on a table in the previous subtest, immediate and delayed testing	No changes
Orientation	Orientation in person, place and time	No changes
Novel Task	A puzzle is laid out within a template, the examiner has to relay the puzzle pieces in the same order, both immediately, and after a delay	Newly developed subtest

Methods

Participants

Twenty-five patients with alcohol-related memory impairment (mean age 56.2; SD=7.0, 17 males) and 25 healthy adults (mean age 42.6; SD=13.0, 16 males) participated in this study. Of the patients, 15 were diagnosed with Korsakoff's

syndrome in agreement with clinical criteria (i.e., APA 1994, Kopelman 2002) and 10 patients with memory deficits and a history of alcohol abuse disorder who did not meet the criteria for Korsakoff's syndrome. None of the patients fulfilled the criteria for alcohol-related dementia (Oslin et al. 1998). All patients were recruited in the Korsakoff Clinic of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands, and their diagnosis was supported by verification of their medical history, neuroimaging findings, psychiatric observation and neuropsychological assessment. The healthy volunteers were recruited via the network of the researchers, i.e. individuals who volunteered to participate in memory research. These included nurses or other non-academic staff of the clinic and relatives or friends of the researchers. None of the healthy participants has a history of neurologic or psychiatric disorders (including substance abuse), and none had subjective cognitive complaints. All were functioning independently in the community. Education level was recorded in accordance with the Dutch educational system using 7 categories (1 = less than primary school, 1-5 years of education; 7 = academic degree; 17-20 years of education). The patients had a lower education level than the healthy participants (mean level patients 3.7; SD=1.6, mean level healthy participants 5.4; SD=0.9; $t(47)=4.9$, $p<0.001$). Premorbid intelligence level was estimated using the Dutch version of the National Adult Reading task (Schmand, Bakker, Saan and Louman 1991). For the patients, mean NART IQ was 95.0 (SD=14.0), mean NART IQ for the controls was 102.1 (SD=14.4). Estimated IQ did not differ between both groups ($t(47)=1.7$). Patients and healthy volunteers differed with respect to age ($t(48)=4.6$, $p<0.001$).

Materials and procedure

All participants completed the Dutch version of the RBMT (Van Balen and Groot Zwaafink 1987) and an authorised Dutch research translation of the RBMT-3 developed to be equivalent to the UK version of this test (Wilson et al. 2008). The administration manual and (verbal) test items of the UK RBMT-3 were translated into Dutch by the first and last author, making sure that individual items were similar in phrasing and complexity. This Dutch translation was then translated back into British English by a native speaker, and both versions were compared and checked by the test publisher. Discrepancies in items were discussed and items were adjusted if necessary. Administration of the RBMT and RBMT-3 was done by trained neuropsychologists. Both tests were administered in a fixed order (RBMT followed by RBMT-3) at different points in time (time between administration of the 2 tests was 5-12 months in the memory-impaired patients and 1-4 weeks in the healthy participants). All patients were tested in the clinic, at least 6 weeks after admittance, making sure that none of the patients was in the acute Wernicke phase and all patients were abstinent from alcohol since

admittance (Walvoort, Wester and Egger, 2013). Healthy volunteers were tested either in the Institute for Psychiatry or in their home environment, all patients were examined in the Institute for Psychiatry. Trained examiners made sure that all participants were examined in a quiet room, without distractions (i.e., no other people present apart from the examiner and participant, no disturbance by mobile phone etc.). Administration and scoring was performed in accordance with the test manual, with the exception of the *Orientation* score that consisted of the Time, Place and Date trials taken together, and the *Names* score that consisted of the First name and Last name trials taken together. This was done for data reduction purposes. Administration of the tests took about the same amount of time in patients and healthy volunteers.

Analyses

In accordance with the RBMT manual (Van Balen and Groot Zwaaftink 1987), performance of each subtest was classified using the 3-point standardized profile score, with 0 reflecting an impaired performance. For the RBMT-3, all raw scores were transformed into standard scores with a normative mean of 10 and an SD of 3 (Wilson et al. 2008). A performance of more than 1.65 SD below the normative mean was considered impaired. For both memory batteries, an impaired performance on a subtest reflects the performance of the lowest 5% of the normative sample (Lezak et al. 2012).

First, the performance of the healthy participants and the patients was compared for all subtests of the RBMT and the RBMT-3 by means of a multivariate analysis of covariance using the raw scores per subtest, adjusting for age and IQ (with Bonferroni correction for multiple comparisons). Next, the frequency of floor and ceiling performances was examined per subtest for both the RBMT and the RBMT-3 by determining the percentage of raw scores of 0 or perfect scores respectively, for the patients and controls separately. This frequency distribution was compared across the two memory batteries using a Wilcoxon signed-rank test. Finally, the number of impaired or unimpaired participants in each group was compared.

Results

Table 2 shows the mean performance of the patient and controls on the subtests of the RBMT and the RBMT-3. No differences in motivation between the patients and the controls were noted, and there were no missing data (all participants completed all subtests of both tests). Significant differences between the two groups were found on most subtests of both batteries.

Table 2 Mean (+SD) performance of the patients and controls on the subtests of the RBMT and RBMT-3, as well as the total score

	RBMT				RBMT-3				F(3,45)	SD
	Healthy		Patients		Healthy		Patients			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Names	3.44	1.08	1.24	1.48	6.48	1.85	3.56	2.84	14.6***	6.9***
Belonging	3.84	0.80	2.60	1.26	7.40	1.47	5.80	2.10	7.6***	2.9
Appointment	1.96	0.20	.60	0.71	2.84	0.99	1.76	1.54	28.4***	3.7
Pictures	9.92	0.28	8.44	2.12	14.64	0.76	13.08	2.45	3.8	3.5
Story (Immediate)	8.36	2.98	4.72	2.90	9.30	3.29	4.32	3.31	10.4***	12.7***
Story (Delayed)	7.30	2.82	3.00	3.35	8.54	3.55	2.84	3.65	12.1***	13.2***
Faces	4.88	0.44	4.20	1.29	13.68	1.31	9.68	2.98	2.6	13.2***
Route (Immediate)	4.92	0.28	3.80	1.50	12.88	0.44	7.08	2.22	5.1	58.9***
Route (Delayed)	4.80	0.50	3.44	1.78	12.84	0.55	5.28	2.67	4.8	71.9***
Message (Immediate)	2.96	0.20	2.32	0.85	5.96	0.20	4.80	1.50	5.3**	4.7
Message (Delayed)	2.92	0.40	1.92	0.95	6.00	0.00	4.08	1.32	8.7***	19.5***
Orientation	9.92	0.28	7.92	2.00	13.10	1.22	10.64	2.00	9.1***	11.4***
Novel Task (Immediate)	-	-	-	-	44.28	4.93	21.68	10.19	-	33.6***
Novel Task (Delayed)	-	-	-	-	16.76	1.20	8.16	4.84	-	24.1***
Total Score	63.94	5.97	44.34	13.41	105.80	10.84	68.20	12.73	18.2***	48.8***

Total Score = RBMT Total Memory Score or RBMT-3 Global Memory Index (GMI)

** p<0.003, *** p<0.001 (Bonferroni-corrected α was set at 0.0038 for the RBMT and 0.0033 for the RBMT-3)

Table 3 shows the frequencies of ceiling performances per subtest (i.e., the percentage of individuals obtaining a perfect performance on a subtest). On all subtests apart from Belonging and Message did the RBMT-3 produce less ceiling effects. Table 4 shows the frequencies of floor performances (a raw score of 0) per subtest. On most subtests of the RBMT and the RBMT-3 a relatively low frequency of floor performances were found. Only on the subtests Names and Appointment did we demonstrate a floor performance in about a quarter of the patients on the RBMT, which was significantly reduced on the RBMT-3 to about 10%. Finally, in Table 5, percentages of impaired (< 5th percentile) individuals in both groups are reported per test version.

Table 3 The frequencies (percentage) of ceiling performance on all individual subtests of the RBMT and the RBMT-3

Subtest	RBMT		RBMT-3		RBMT	RBMT-3	Z
	Healthy	Patients	Healthy	Patients	Total	Total	
Names	76%	16%	44%	8%	46%	26%	-2.4*
Belonging	96%	36%	80%	32%	66%	56%	-1.3
Appointment	96%	12%	40%	24%	54%	32%	-2.5*
Pictures	92%	44%	76%	32%	68%	54%	-2.1*
Faces	92%	60%	36%	0%	76%	18%	-5.4***
Route (Immediate)	92%	44%	92%	0%	68%	46%	-2.8**
Route (Delayed)	84%	40%	92%	0%	62%	46%	-2.1*
Message (Immediate)	96%	52%	96%	32%	74%	64%	-1.5
Message (Delayed)	96%	36%	100%	20%	66%	60%	-1.1
Orientation	92%	24%	48%	4%	64%	26%	-4.1***
Novel Task (Immediate)	-	-	12%	0%	-	6%	-
Novel Task (Delayed)	-	-	96%	8%	-	52%	-

Z = statistical comparison between RBMT and RBMT-3 (total group taken together)

* p<0.05; ** p≤0.01; *** p<0.001

Table 4 The frequencies (percentage) of floor performance on all individual subtests of the RBMT and the RBMT-3

Subtest	RBMT		RBMT-3		RBMT	RBMT-3	Z
	Healthy	Patients	Healthy	Patients	Total	Total	
Names	4%	48%	0%	20%	26%	10%	-2.5*
Belonging	4%	8%	0%	4%	6%	2%	-1.4
Appointment	0%	52%	0%	24%	26%	12%	-2.6**
Pictures	0%	0%	0%	0%	0%	0%	0
Faces	0%	4%	0%	0%	2%	0%	-1.0
Route (Immediate)	0%	4%	0%	0%	2%	0%	-1.0
Route (Delayed)	0%	12%	0%	0%	6%	0%	-1.7
Message (Immediate)	0%	4%	0%	4%	2%	2%	0
Message (Delayed)	0%	4%	0%	0%	2%	0%	-1.0
Orientation	0%	0%	0%	0%	0%	0%	0
Novel Task (Immediate)	-	-	0%	0%	-	0%	
Novel Task (Delayed)	-	-	0%	0%	-	0%	

Z = statistical comparison between RBMT and RBMT-3 (total group taken together)

* p<0.05; ** p≤0.01; *** p<0.001

Table 5 Percentage of impaired (< 5th percentile) individuals for the RBMT and the RBMT-3

Subtest	RBMT		RBMT-3	
	Healthy	Patients	Healthy	Patients
Names	18%	72%	4%	40%
Belonging	4%	64%	4%	24%
Appointment	4%	84%	0%	48%
Pictures	8%	56%	8%	32%
Story (Immediate)	n.a.	n.a.	0%	56%
Story (Delayed)	20%	76%	4%	64%
Faces	8%	40%	0%	36%
Route (Immediate)	8%	56%	0%	52%
Route (Delayed)	20%	60%	0%	68%
Message (Delayed)	8%	68%	0%	36%
Orientation	8%	64%	8%	68%
Novel Task (Immediate)	-	-	0%	52%
Novel Task (Delayed)	-	-	0%	48%

n.a. = no separate norms available for this subtest

Discussion

Aim of the present study was to compare a group of healthy participants and a group of cognitively impaired patients on the RBMT and the RBMT-3. First, we demonstrated that floor effects were infrequent on the RBMT-3, and that significantly less floor performances were found on the subtests Names and Appointment of the RBMT-3 compared to the RBMT, in which almost a quarter of participants performed at floor level on these subtests. With respect to ceiling performance, we showed that the RBMT-3 is a substantial improvement over the RBMT, as a high number of perfect scores were obtained on most RBMT subtests. Whereas the number of perfect scores was significantly reduced on the RBMT-3 subtests Names, Appointment, Belonging, Pictures, Faces, Route recall and Orientation, ceiling effects were present still in a large percentage of participants (up to 64%). Ceiling and floor effects are undesirable in neuropsychological tests, as they are designed to examine individual differences in task performance even in healthy participants, and may limit the applicability of the test (Strauss et al. 2006). This in contrast to screening instruments such as the Mini-Mental State Examination (MMSE; Folstein et al. 1975) that have been designed to

diagnose a specific disorder, such as Alzheimer's dementia and on which participants without the disorder may obtain a (near-)perfect score.

Examining the percentage of participants performing in the impaired range on the different subtests (i.e., below the 5th percentile compared to the normative data), the RBMT contains a few problematic subtests on which a high percentage of cognitively unimpaired adults performs in the impaired range. That is, on the delayed tests of the Story and Route subtest, as well as the Names subset, about 20% of healthy volunteers is classified as impaired. The RBMT-3 is a substantial improvement in this respect, as the percentage of healthy participants classified as impaired lies between 0 and 8% (note that by definition, 5% is expected to be impaired, i.e., all participants performing below the 5th percentile). Also, the number of impaired patients is lower on the RBMT-3 than on the RBMT.

With respect to the newly added subtest, Novel Task, no substantial ceiling or floor effects were found on the immediate trial of this subtest, but a perfect performance was found in half of the participants after delayed testing. Still, none of the controls performed in the impaired range on this test, whereas about half of the patients performed in the impaired range on this subtest. As this subtest measures procedural learning for which no other neuropsychological tests are available with normative data, it is as such a valuable addition to the Rivermead memory battery.

With respect to the limitations of the current study, it should be noted that the time between the administration of the two RBMT variants differed for the controls and the patients. One could argue that recovery may have taken place in the patients, making the two administrations not comparable. However, all patients were in the chronic stable phase in which no cognitive recovery is to be expected (i.e., more than 6 weeks after admission; Walvoort et al., 2013). Furthermore, our heterogeneous and relatively small patient sample makes it not possible to examine Korsakoff and non-Korsakoff patients with alcohol-abuse disorder separately. However, we would like to stress that we deliberately selected a heterogeneous sample with respect to cognitive status (from unimpaired controls to mild memory deficits and severe amnesia), as ceiling effects on cognitive tests are less common in cognitively patients, whereas floor effects rarely occur in healthy individuals. Finally, as the number of items differ between the RBMT and the RBMT-3 on many subtests, we could not perform reliability analyses directly comparing both versions of the test (e.g., by computing intra-class correlations).

The RBMT has been used in previous studies in Korsakoff and alcohol-related cognitive disorders (Oudman et al. 2012; Van Balen et al. 1998; Kopelman et al. 1989), but to our knowledge, none of these studies examined the performance pattern across the different subtests. Also, no studies have been published yet that have used the RBMT-3, neither in patients with alcohol-related cognitive

disorders nor in other patients samples. More research is needed with the RBMT-3, especially as it is one of the few memory test batteries that may have ecological validity, that is, predict everyday functioning. Previous studies have demonstrated the ecological validity of the RBMT. For example, performance on the RBMT was predictive for social functioning in patients with schizophrenia (Guaianna et al. 2004), and was also related to functional impairment in patients with multiple sclerosis (Higginson et al. 2000). The addition of a subtest measuring procedural learning may even increase its predictive value for everyday functioning, but future studies have to investigate this. Moreover, although the original RBMT has been used in a range of psychiatric disorders, it remains to be studied whether the RBMT-3 is also applicable for the assessment of memory dysfunction in patients with other psychiatric disorders, as they may have milder forms of memory deficits compared to the currently studied sample.

In all, this is the first study published using the RBMT-3, in which we also directly compared the performance on the RBMT-3 with the RBMT. With respect to ceiling and floor effects, the RBMT-3 is a substantial improvement over the original RBMT. Increasing the number of items in several subtests of the RBMT-3 has resulted in less participants performing at or near the subtest's ceiling, as to be expected, but on the other hand did also result in lower frequencies of floor performances. This is highly relevant for clinical practice, as floor and ceiling effects seriously hamper test validity. In addition, the RBMT-3 classifies less healthy participants as impaired, which was especially problematic on the Story, Route and Names subtests of the original RBMT.

Key points

- The third edition of the Rivermead Behavioural Memory Test (RBMT-3) is a substantial improvement over the original RBMT with respect to ceiling and floor performances
- Using the RBMT-3, less healthy volunteers are being classified as memory impaired compared to the original RBMT
- More research is needed on the ecological validity of the RBMT-3 in patients with alcohol-related memory deficits, as well as in other patient groups

Disclosure of interests

The RBMT-3 translation was authorized by Pearson Assessment B.V, the Netherlands. Pearson also provided the test materials for the RBMT-3, but was in no way involved in the study design, analysis and writing of this paper. None of the authors has any conflicts of interest to declare.

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7

CHAPTER

Applicability of the RBMT-3 in Korsakoff's syndrome and chronic alcoholics

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Abstract

Purpose: To examine the applicability of the newly developed Rivermead Behavioural Memory Test – Third Edition (RBMT-3) as a supposedly ecologically valid memory test in patients with alcohol-related cognitive disorders.

Patients and methods: An authorized Dutch translation of the RBMT-3 was developed, equivalent to the UK version, and administered in a total of 151 participants: 49 patients with amnesia due to alcoholic Korsakoff's syndrome, 49 patients with cognitive impairment and a history of chronic alcoholism, not fulfilling the Korsakoff criteria and 53 healthy controls. Between-group comparisons were made at subtest level, and the test's diagnostic accuracy was determined.

Results: Korsakoff patients performed worse than controls on all RBMT-3 subtests (all p -values <0.0005). The alcoholism group performed worse than controls on most (all p -values <0.02), but not all RBMT-3 subtests. Largest effects were found between the Korsakoff patients and the controls after delayed testing. The RBMT-3 had good sensitivity and adequate specificity.

Conclusion: The RBMT-3 is a valid test battery to demonstrate everyday memory deficits in Korsakoff patients and non-Korsakoff patients with alcohol abuse disorder. Especially the performance on subtests relying on orientation, contextual memory and delayed testing are impaired in Korsakoff patients. Our findings provide valuable information for treatment planning and adjustment in patients with alcohol-related cognitive impairments.

Introduction

Chronic alcohol abuse may result in brain damage and cognitive deficits, such as impairment in memory function, but also deficits in executive functions. For example, in Korsakoff's syndrome, chronic thiamine deficiency may result in bilateral lesions of the diencephalon, including the mammillary bodies and thalamus, which may produce severe anterograde and (to a lesser extent) retrograde amnesia (Kopelman, 2002). Specifically, the episodic aspect of long-term memory is impaired in Korsakoff patients (Kessels & Kopelman, 2012), like memory for contextual information as such (e.g., spatial information or temporal-order memory) and the ability to associate context and target information, that is, the 'what, where and when' of everyday experiences. Milder forms of memory deficits have been reported in non-Korsakoff chronic alcoholics, due to the neurotoxic nature of alcohol that may result in global brain atrophy (Green et al., 2010).

A wide variety of neuropsychological tests is available to examine memory function in brain injured adults, such as the California Verbal Learning Test (CVLT), the Rey Auditory Verbal Learning Test (RAVLT) and the Wechsler Memory Scale – Fourth edition (WMS-IV) (Lezak et al., 2012). However, many of these tests have been criticized as they may lack the ability to predict daily-life functioning (often referred to as ecological validity; Wilson, 1993). The Rivermead Behavioural Memory Test (RBMT) has been specifically developed as a measure of everyday memory function (Wilson et al., 1989). Also, parallel versions of the test were developed, making this memory battery applicable for treatment outcome assessment. The RBMT has been widely used for examining patients with alcohol-related cognitive disorders, and has been recommended for use in Korsakoff patients given its relevance for daily memory problems (Smith & Hillman, 1999). Duffy and O'Carroll (1994), for instance, demonstrated that compared to other memory tests, the RBMT resulted in the largest effect sizes when comparing Korsakoff patients with other neuropsychiatric patients (i.e., patients with schizophrenia). Several other studies also reported profound deficits in Korsakoff patients compared to normative data (Brunfaut & d'Ydewalle, 1994; Kopelman, 1989). Furthermore, the RBMT has been used to examine treatment effects of fluvoxamine in Korsakoff patients on memory function (O'Carroll et al., 1994). The RBMT has also been applied in the study of non-Korsakoff alcohol users. For example, Van Balen and colleagues (1996) have examined a heterogeneous group of alcohol-related cognitive disorders, showing poor performances on the RBMT. Others have administered the RBMT in long-abstinent alcoholics without KS, showing an unimpaired memory performance which may be due to recovery (Mlinarics et al., 2009).

However, while successful and widely used, the original RBMT suffered from a lack of sensitivity on some subtests (Wilson et al., 1985), as many subtests consisted of only a small number of items. The third edition of this test (RBMT-3) has overcome this problem by updating a number of stimuli, extending the number of trials in several subtests and by adding a new subtest (Wilson et al., 2008). The RBMT-3 consists of a number of subtests, each of which addresses an important aspect of everyday memory function. For instance, patients have to remember a route, a short story or a message, must recall photographs of people, and have to remember to retrieve a personal belonging at the end of the examination. Also, orientation is tested and a newly developed puzzle subtest is included, in which participants have to relay puzzle pieces in a specific order. Thus, the RBMT-3 assesses verbal and nonverbal episodic memory, spatial memory, and aspects of prospective memory, and procedural memory. In several subtests, memory is tested both immediately after stimulus presentation and after a filled delay. The RBMT-3 has been examined in relatively small samples of patients with traumatic brain injury, stroke, encephalitis and neurodegenerative diseases, e.g. Alzheimer's disease (Wilson et al., 2008). To date, however, no studies have been published using the RBMT-3 in patients with alcohol-related cognitive deficits, while the original RBMT – despite its limitations – is still being used clinically. The present study examines the memory profile of amnesic patients with alcoholic Korsakoff's syndrome using the RBMT-3 as a supposedly ecologically valid memory test battery, comparing their performance to non-Korsakoff chronic alcoholics (with mild cognitive impairments) and healthy controls.

Material and methods

Study Design and Participants

We have performed a case-control study using a convenience sample of patients with alcohol-abuse disorder that were diagnosed with Korsakoff's syndrome or had less severe memory deficits, as well as matched healthy controls. Recruited patients were inpatients of the Korsakoff clinic of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. The Korsakoff patients fulfilled the DSM-IV-TR criteria for alcohol-induced persisting amnesic disorder (291.1), that is, a memory deficit had to be present, that results in severe deficits in social functioning, in the absence of delirium or dementia, with a history of alcohol-abuse disorder. In addition, the criteria for alcoholic Korsakoff's syndrome¹ had to be met: evidence for a history of Wernicke encephalopathy, confabulation behavior and evidence for malnutrition or thiamine deficit. The patients with

cognitive impairment and a history of chronic alcoholism (DSM-IV-TR Alcohol Dependence, 303.90) and fulfilled the DSM-IV-TR criteria for cognitive disorder not otherwise specified (294.9). All diagnoses were supported by medical history, psychiatric assessment, neuropsychological testing covering all major cognitive domains and neuroradiological findings, and all patients had been abstinent for alcohol for at least six weeks. None of the patients had any evidence for brain abnormalities that could account for their condition apart from atrophy or white-matter lesions associated with the chronic alcohol abuse. None of the participants fulfilled the proposed criteria for alcohol-related dementia (Oslin et al., 1998), and none of the participants had any hearing problems, language or communication deficits, or visual agnosia that could confound the performance on memory tests.

Healthy participants were recruited from the clinic's staff, databases of healthy volunteers, and the network of the researchers. Exclusion criteria for controls were a psychiatric or neurologic history or subjective memory complaints (self report). Education level was assessed using 7 categories in accordance with the Dutch educational system (1 = less than primary school; 7 = university degree). The Dutch version of the National Adult Reading Task (NART) was administered to estimate verbal intelligence level (IQ) (Schmand et al., 1991).

Materials

An authorized Dutch translation of the RBMT-3 was constructed to be equivalent to the previously published UK version of this test (Wilson et al., 2008). Test items and test instructions were translated into Dutch and back translated into British English by native speakers. Differences in phrasing or meaning were resolved by discussion, resulting in a Dutch-language research version of the RBMT-3 that was used in the current study. The RBMT-3 consists of ten subtests (maximum score between brackets): Names (remembering the first and second names of two portrait photos; max = 8), Belongings (remembering to ask for two personal belongings at the end of the test session; max = 8), Appointments (asking two questions when an alarm rings 25 minutes later; max = 4), Picture Recognition (delayed recognition of line drawings; max = 15), Story (immediate and delayed recall of a short news story; max = 2 × 21), Faces (delayed recognition of photographs of faces; max = 15), Route (immediate and delayed recall of a short route in the examination room; max = 2 × 13), Message (immediate and delayed remembering to pick up an envelope and book; max = 2 × 6), Orientation and Date (orientation to person, place and time; max = 14), and Novel Task (immediate and delayed recall of a puzzle pieces laid in a specific order within a template; max for three immediate trials = 51; max for delayed recall = 17).

Administration of the RBMT-3 was performed in accordance with the test's manual by trained neuropsychologists or research assistants and took approximately 30 minutes. In addition to the raw scores on the subtests, the Global Memory Index (GMI) was computed as an overall memory performance measure.

Analysis

Multivariate analyses of variance (General Linear Model) were performed using the performance on the individual subtests of the RBMT-3 for the three groups. Bonferroni-corrected post-hoc analyses were performed to compare the specific groups (KS-CON, ALC-CON and KS-ALC), all post-hoc p-values reported are SPSS-adjusted p-values, and effect sizes (Cohen's d) were computed. Additionally, receiver operating characteristic (ROC) analyses were performed on the GMI to determine the test's diagnostic accuracy, comparing the KS and the ALC group and the ALC and CON groups. Cut-off scores for the GMI were determined that had good sensitivity (≥ 0.8) and adequate specificity (≥ 0.6) (Kessels et al., 2009). All analyses were performed using IBM SPSS Statistics Version 19. Alpha was set at 0.05 for all analyses.

Table 1 Demographic variables for the Korsakoff patients (KS), the cognitively impaired alcoholics (ALC) and the healthy controls (CON)

	KS	ALC	CON
Age (years; mean \pm SD)	55.6 (6.4)	55.0 (6.7)	54.9 (7.2)
Education level (mode+range)	4 (2-6)	4 (1-7)	5 (3-7)
NART-IQ (mean \pm SD)	90.3 (14.0)	90.9 (16.8)	97.2 (10.4)
Sex (m:f)	37:12	35:14	27:26

Abbreviation: NART, National Adult Reading Test.

Results

A total of 151 participants enrolled in this study, consisting of 49 patients with Korsakoff's syndrome (KS), 49 patients with cognitive impairment and a history of chronic alcoholism (ALC), and 53 healthy controls (CON). Table 1 shows the demographic variables for the three groups of participants. The groups did not differ with respect to age ($F(2,148)=0.2$), but differed with respect to education level ($\chi^2(2)=9.6$, $p=0.008$) and IQ ($F(2,138)=3.4$, $p=0.04$). The healthy controls had on average a higher education level than the KS patients (Mann-Whitney U =

979.5, $Z=2.6$, $p=0.011$) and the ALC group ($U=1032.5$, $Z=2.2$, $p=0.035$), although in all three groups most participants had an average education level (categories 4 and 5). Bonferroni-corrected post-hoc tests comparing the KS, ALC and CON groups directly did not reveal significant IQ differences (all p -values >0.05). The groups differed with respect to sex distribution ($\chi^2(2)=7.9$, $p=0.02$), with fewer women KS and ALC patients compared to the healthy control group ($U=907.5$, $Z=2.3$, $p=0.021$; $U=820.5$, $Z=2.9$, $p=0.003$ respectively).

Table 2 shows the results of the individual RBMT-3 subtests for the three groups. GLM analysis taking all subtests together demonstrated an overall main effect of Group ($F(28,272)=7.4$, $p<0.0005$). Subsequent multivariate GLM analyses on the individual subtests demonstrated an overall Group effect on all individual subtests (all F -values > 10.7 , all p -values <0.001). Post-hoc analyses comparing the patient groups with the controls, demonstrated a significant worse performance than controls on all subtests for the KS group (all p -values <0.0005). The ALC group performed worse than controls on most subtests (all p -values <0.02), but not on the subtests Picture Recognition, Story Recall – Delayed, Messages – Immediate, and Orientation, on which the performance did not differ significantly from controls. Directly comparing both patient groups showed a worse performance in the KS group compared to the ALC group on most subtests (all p -values <0.001), except on the subtest Story Recall – Immediate on which no statistically significant difference was found ($p=0.10$). With respect to effect sizes, large effects were found on all subtests, with the largest differences between the KS and CON group after delayed testing on Picture Recognition, Face Recognition, Route Recall, Messages, and the Novel Task, as well as on the subtests Belongings, Appointments and Orientation. Adjusting the analyses by including education level as a covariate did not alter the results (data not shown).

ROC analyses revealed that the RBMT-3 GMI had a statistically significant diagnostic accuracy in distinguishing KS patients from ALC patients ($AUC=0.85$; 95%CI 0.78-0.93; $p<0.0005$). A cut-off score of $GMI<67.5$ had a sensitivity of 0.80 and a specificity of 0.69. The GMI could also distinguish ALC patients from healthy controls ($AUC=0.83$; 95%CI 0.75-0.91; $p<0.0005$). A GMI cut-off of 87.5 had a sensitivity of 0.80 and a specificity of 0.62.

Table 2 Performance (mean number of correct items) on the RBMT-3 subtests for the Korsakoff patients (KS), the cognitively impaired alcoholics (ALC) and the healthy controls (CON)

RBMT-3 subtest	KS (N=49)			ALC (N=49)			CON (N=53)		
	Mean	SD	d	Mean	SD	d	Mean	SD	d
Names	2.27	2.32	-1.81	3.98	2.59	-0.89	5.66	1.88	
Belongings	4.24	1.92	-2.21	5.90	2.10	-0.82	6.87	1.19	
Appointments	.94	1.05	-2.46	2.31	1.40	-0.99	3.23	0.93	
Picture Recognition - delayed	12.16	2.78	-4.03	14.08	1.30	-0.93	14.66	0.62	
Story Recall - immediate	3.74	2.42	-0.92	4.91	2.79	-0.51	6.37	2.85	
Story Recall - delayed	1.56	2.25	-1.39	4.02	2.92	-0.45	5.19	2.61	
Face Recognition - delayed	8.86	3.27	-3.57	11.27	2.48	-1.64	13.32	1.25	
Route Recall - immediate	6.20	2.42	-1.70	8.27	2.60	-0.90	10.58	2.58	
Route Recall - delayed	4.78	2.58	-2.38	7.80	2.87	-1.20	10.89	2.57	
Messages - immediate	4.57	1.67	-1.32	5.29	.91	-0.44	5.64	0.81	
Messages - delayed	2.94	1.91	-2.55	4.69	1.40	-0.81	5.51	1.01	
Orientation and date	8.76	2.85	-2.97	11.66	1.44	-0.59	12.38	1.22	
Novel Task - immediate	18.92	10.45	-1.95	27.92	10.79	-0.93	36.19	8.86	
Novel Task - delayed	5.47	3.95	-2.67	11.31	4.81	-0.81	13.85	3.14	
GMI	61.16	8.54	-2.63	76.00	11.96	-1.39	92.58	11.94	

Abbreviations: RBMT-3 = Rivermead Behavioural Memory Test – Third Edition; GMI = Global Memory Index.
d = Cohen's *d*, comparing patients with the controls

Discussion

Aim of the present study was to examine whether the RBMT-3 can be used to demonstrate alcohol-related memory deficits, and whether it is able to distinguish patients with KS from patients with more subtle alcohol-related memory deficits, and the latter from healthy controls. Our findings clearly show that both patients with KS and non-Korsakoff-alcoholics with cognitive deficits perform worse than matched controls on the RBMT-3. Looking at the pattern of impairments, largest effect sizes were found on tests of delayed recall, orientation, as well as cued and uncued prospective memory in the KS patients. This is in agreement with the presumed neural substrate of Korsakoff's syndrome, that is, diencephalic lesions in the mammillary bodies and the thalamus (Pitel et al., 2012). Also, some studies have reported hippocampal atrophy in KS patients (Sullivan & Pfefferbaum, 2009; Visser et al., 1999). As a result, long-term storage of new information is hampered by a deficit in consolidation (Kopelman et al., 2009), which strongly relies on medial-temporal lobe and diencephalic structures (Kessels & Kopelman, 2012). Looking at the type of task that is tested after a delay, recognition tasks such as Face Recognition or Picture Recognition do not improve the memory performance, which also points towards a consolidation deficit rather than impaired retrieval, as in the latter recognition performance is expected to improve substantially (Duchnik et al., 2002). The deficit in delayed memory ("rapid forgetting") has also been directly associated with lesions of KS patients in the diencephalon and hippocampus (Visser et al., 1999). Deficits on Route Recall and Messages in KS patients may be related to an impaired memory for contextual information, notably spatial memory and object-context integration (Kessels & Kopelman, 2012). The impaired performance on the Novel Task may partly be due to a deficit in motor or procedural learning. While implicit learning in KS has been shown preserved, e.g., on visuoperceptual tasks or simple motor learning (Fama et al., 2006; Van Tilborg et al., 2011), impaired performance on more complex procedural tasks, such as spatial pattern learning or a Tower paradigm, have been demonstrated in KS patients (Beaunieux et al., 2013; Van Tilborg et al., 2011). Also, performance on the Novel Task may rely on non-procedural processes, such as spatial working memory (in the immediate test) and visuospatial episodic recall after delayed testing. Finally, prospective memory deficits in KS patients have been linked to prefrontal dysfunction (Oscar-Berman, 2012), or may be explained by the general inability to encode and consolidate information over longer periods of time, although studies are lacking examining prospective memory in more detail in KS patients.

With respect to the non-Korsakoff alcoholics, effect sizes in the ALC group compared to the controls were smaller than in the KS group, and the performance did not differ from the healthy participants on all subtests. That is, orientation, memory for pictures, messages and prose recall were at control level. KS patients also performed worse than the ALC group on all but one RBMT-3 subtest. These results are in agreement with a previous study that also demonstrated unimpaired performance on the original RBMT subtest Story Recall in chronic alcoholics (Uekermann et al., 2003). In contrast, a study in long-abstinent chronic alcoholics reported an unimpaired performance on all original RBMT subtests (Mlinarics et al., 2009). The discrepancy with our study in which we show memory deficits on many RBMT-3 subtests in non-Korsakoff chronic alcoholics could be due to recovery, as their patients have been abstinent over 6 months, while the chronic alcoholics in the present study sample had been abstinent for 6 weeks. Moreover, a recruitment bias may be present, as the non-Korsakoff chronic alcoholics in our clinic are being referred because of possible cognitive deficits. Alternatively, these apparently mixed results may also be the result of the relative insensitivity of the original RBMT. That is, previously we showed by directly comparing the performance on the RBMT and the RBMT-3 that the latter is more sensitive in detecting alcohol-related memory deficits and that ceiling effects are present on some subtests (Wester et al., 2013). The effect sizes of the ALC group in the present study were in the moderate to large range (Cohen, 1988), indicating that while the memory impairments on the RBMT-3 are not as profound as in KS, they are clinically relevant and may hamper everyday functioning.

The Global Memory Index of the RBMT-3 showed good diagnostic accuracy to distinguish KS patients from milder forms of memory deficits after alcohol-abuse disorder, and the latter group from healthy controls. However, these results should be interpreted with some caution, as there may be a risk of circularity here. That is, although the diagnoses were made based on medical history, radiological findings, and extensive cognitive testing, also in non-memory domains and using other memory tests such as the California Verbal Learning Test, having 'amnesia' is part of the diagnostic criteria for KS which has to be diagnosed using neuropsychological tests. Still, the here presented cut-off values may be useful for clinicians working with patients with alcohol-abuse disorder that are suspect of having memory deficits.

While the Rivermead Behavioural Memory tests batteries have been developed to assess everyday memory performance presumably adopting a more ecologically valid approach, the ecological validity of this test battery has also been criticized. For example, Koltai and colleagues (1996) compared the performance of a group of patients that had been exposed to neurotoxic agents

on the revised Wechsler Memory Scale (WMS-R, a 'non-ecological' memory battery) and the RBMT, and could neither demonstrated significant differences between the two tests, nor establish any incremental value of administering a combination of the two memory batteries. Others (Higginson et al., 2000) showed that RBMT total score could not significantly predict functional status in patients with multiple sclerosis (MS). In that study, both delayed RBMT Story Recall and delayed recall of the CVLT predicted functional status at subtest level, questioning the added value of ecologically valid memory tests. However, in that study some RBMT subtests were not administered because of ceiling effects in MS patients, which may also explain this lack of statistical significance. With respect to the RBMT-3, only modest correlations between the GMI and self- and proxy-rated versions of a rating scale for everyday memory problems (Wilson et al., 2008). However, no studies have yet been performed in people with alcohol-related cognitive disorders or in any other patient sample using the RBMT-3 that specifically examine the test's predictive validity for other ecological outcome measures, such as return to work or ability to live independently in people with alcohol-related cognitive disorders or any other patient sample. Finally, it should be noted that not all aspects of memory can be examined using the RBMT-3. That is, the test does not include subtests assessing working memory or semantic memory, which would be relevant as deficits in these memory functions have also been demonstrated in Korsakoff patients (Bardenhagen et al., 2007; Kopelman et al., 2009; Van Geldorp et al., 2012).

Our results showing memory deficits in patients with alcohol-abuse disorder also emphasize concurrent findings that treatment in patients with alcohol-abuse disorder should not only be limited to the addiction itself. That is, the cognitive deficits should be taken into account as well (Walvoort et al., 2012), for example by incorporating strategy or other compensatory trainings based on cognitive rehabilitation principles. Moreover, the presence of severe cognitive deficits also requires adjustment of the available treatment programs in addiction care (Bates et al., 2002). For example, group psychotherapy sessions may be less effective in cognitively-impaired patients, as a lot of information is being shared. Also, cognitive deficits affect the applicability of cognitive-behavioral therapy, which relies on self-reflection, sharing of conceptualizations, and explicitly remembering stressful situations. Finally, a detailed profile of everyday memory (dys)function provides specific information about an individual patient that can guide care professionals and optimize clinical management.

Conclusion

Our present results show that the RBMT-3 seems to have clinical relevance for the assessment of severe memory deficits in KS patients on the one hand and milder memory impairments associated with chronic alcohol abuse on the other. Especially the performance on subtests relying on orientation, contextual memory and delayed testing are impaired in KS patients, related to the presumed underlying dysfunction in hippocampal-diencephalic brain regions. The deficits in the ALC group are less severe, and on some subtests even at control level. Our findings stress that cognitive impairment should on the one hand also be considered in the treatment of patients with alcohol-abuse disorder (e.g., using cognitive rehabilitation), and available addiction therapies should be adjusted for patients with limitations in cognitive processing capacities. Future studies should examine the ecological validity (i.e., predictive value) of the RBMT-3 for everyday function in these patients. In addition, the validity of changes in performance on the RBMT-3 parallel version as an outcome measure of, for example, cognitive rehabilitation or spontaneous recovery in non-Korsakoff alcoholics, remains to be determined.

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8

CHAPTER

Predicting memory impairment on the RBMT-3 using the MoCA in alcohol-related cognitive disorder

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Abstract

Objective: The Montreal Cognitive Assessment (MoCA) provides an indication of overall cognitive functioning and aims to measure several cognitive domains, such as memory, visuospatial abilities, executive function, attention and concentration, language, fluency, and orientation. It has been found sensitive to detect the (mild) cognitive impairment in patients diagnosed with substance dependence but it is unknown whether the MoCA is able to differentiate between mild and more severe forms of memory impairment, such as differentiating Korsakoff patients, who have severe amnesia, orientation difficulties and executive dysfunctions, from chronic alcoholics, who have cognitive deficits, but do not fulfill the criteria for KS.

Method: In order to examine discriminatory power of the MoCA and predictive capacities for the severity of amnesia, both the MoCA and the widely-used Rivermead Behavioural Memory Test (RBMT-3) were administered to 20 patients with Korsakoff syndrome, to 26 patients with non-Korsakoff alcohol related cognitive impairment, and to 33 healthy control subjects. *Results:* Results suggests that the MoCA has discriminatory power in the diagnosis of patients with alcohol-related cognitive impairments and predictive capacities with regard to the severity of memory impairment. For all comparisons, specific cut-off scores were established.

Conclusions: While it can be concluded that the MoCA is a useful screening instrument, it should be stressed that it cannot substitute a more extensive neuropsychological assessment which is essential to the detailed analysis of the cognitive profile and, consequently, for adequate treatment selection.

Introduction

Memory plays an essential role in everyday tasks, such as speaking, reading, writing, planning, and understanding, and is indispensable for adequate human functioning (Baddeley et al., 2002). Consequently, amnesic disorders are likely to have great impact on almost all areas of daily life. Such disorders can be caused by several neurological and neuropsychiatric diseases such as dementia, brain tumor, stroke, cerebral trauma or Korsakoff's syndrome (Mesulam, 2008). The classification of memory disorders and particularly, the differentiation of milder from more severe forms, not only supports the diagnostic process but is also a prerequisite for selecting interventions fitting the degree of impairment.

Extensive neuropsychological assessment can be used to investigate the profile and severity of cognitive impairments in multiple cognitive domains (Lezak et al., 2012). However, such an assessment may be costly and not feasible in all clinical settings due to time constraints. As a result, screening instruments for the detection of cognitive impairments have been developed, such as the Mini-mental State Examination (Folstein et al., 1975). However, many of these screening instruments have been criticized due to lack of sensitivity and specificity or poor reliability (review MMSE). According to Shulman (2000), an ideal screening instrument meets the following criteria: (a) short administration time, (b) easy to score, and (c) adequate levels of sensitivity, specificity, and validity. An example of a promising short screening instrument is the Montreal Cognitive Assessment (MoCA), which provides an indication of overall cognitive functioning (Nasreddine et al., 2005) and aims to measure several cognitive domains, such as memory, visuospatial abilities, executive function, attention and concentration, language, fluency, and orientation.

The MoCA has been found to be sensitive to less severe forms of cognitive disorders that can occur in the context of neurodegenerative diseases (e.g., Mild Cognitive Impairment; MCI) and several studies have showed that the MoCA can distinguish patients with MCI from healthy controls (Nasreddine et al., 2005). However, different cut-off scores have been reported. Fujiwara et al. (2010), for instance, report an optimal cut-off score of 25 (out of the maximum score of 30) for detecting MCI (Fujiwara et al., 2010), while others reported a cut-off score of 23 (e.g., Lee et al., 2008). This might be attributed to differences in educational level of the participants since the number of educational years has been reported to influence performance on the MoCA (Nasreddine et al., 2005). Whether other patient characteristics would lead to different levels of sensitivity and specificity, remains equivocal (Thissen et al., 2010).

Since there is evidence for the MoCA being able to tap mild memory impairments and to adequately classify patients with MCI, it would be useful to

know if it can be used for the classification of other patient groups with cognitive disorders, specifically in patients suspect of cognitive impairment due to alcohol-use disorder. The MoCA has been found sensitive to detect the (mild) cognitive impairment in patients diagnosed with substance dependence (Copersino et al., 2009). It remains to be studied, however, whether in these patients with substance dependence, the MoCA is able to differentiate between mild and more severe forms of memory impairment, such as differentiating patients with Korsakoff's syndrome (KS) who have severe amnesia, orientation difficulties and executive dysfunction (Kopelman, 2002) from chronic alcoholics who have cognitive deficits, but do not fulfill the criteria for KS.

Korsakoff syndrome can be defined as 'an abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient, resulting from nutritional depletion, notably thiamine deficiency' (Kopelman 2002, p. 2153). In the Western world, Korsakoff syndrome is usually found in chronic alcoholics. Apart from the study of Blansjaar and colleagues (1987), who reported a prevalence of 4.8 per 10.000 inhabitants diagnosed with Korsakoff's syndrome in the city of The Hague, Netherlands, no recent Dutch epidemiological data are available. Based on these data, the number of Korsakoff patients in the Netherlands is estimated between 5.000 and 15.000 individuals.

The present study examines the sensitivity and specificity of the MoCa in a group of participants with suspected memory deficits due to alcohol-use disorder, comparing the MoCA with a more extensive assessment of memory function using the third version of the Rivermead Behavioural Memory Test (RBMT-3) as gold standard. The RBMT-3 is a test battery with high ecological validity, enabling the detection of disorders in everyday memory functioning. In addition, the test measures the severity of a memory disorder, which is of special interest to this study. Its subtests reflect everyday memory tasks, such as memorizing news reports, names, routes, appointments, and recognition of pictures and faces (Wilson et al., 2008). This study has two objectives. First, we examine whether the MoCA can distinguish between two patient groups with cognitive disorders and a healthy control group, and particularly addresses the question to what extent it is able to classify patients with Korsakoff's syndrome and patients with cognitive impairment due to excessive alcohol use. Second, we will examine whether the MoCA can be used as an index of the severity of a memory disorder. Finally, the optimal cut-off scores for the MoCA will be calculated.

Method

Subjects

A total of 79 adults, aged 38-72 years, participated in this study. Patients (n=46) were admitted to the Korsakoff clinic of the Vincent Van Gogh Institute for Psychiatry in Venray, The Netherlands. Reason for admission was suspected cognitive impairments due to alcohol-use disorder. Of these 46 patients, twenty were diagnosed with KS, and 26 subjects with alcohol-related cognitive impairment (not fulfilling the criteria for KS). The KS diagnosis was given when anterograde amnesia was present in a history of chronic, heavy drinking, and malnutrition. KS patients had to fulfill the DSM-IV-TR criteria for alcohol-induced persisting amnesic disorder. The diagnoses were supported by extensive neuropsychological assessment, medical history, psychiatric and neuroradiological examination and observations by a multidisciplinary team, and were agreed upon in a multidisciplinary meeting. All patients with alcohol-related cognitive impairments had a history of long-term heavy drinking, and were referred by addiction care centers. They fulfilled the DSM-IV-TR criteria for alcohol dependence and did not have the severe memory deficits of Korsakoff's syndrome. In addition to these patients, 33 healthy volunteers were included. Potential volunteers with a history of neurological or psychiatric disease, or documented alcohol or drug addictive disorders (self report) were excluded from participation. Table 1 presents the demographic data of the three groups.

Table 1 Demographical variables of healthy adults, patients with alcohol-related cognitive impairments, and patients with Korsakoff syndrome.

	Group			<i>p</i>
	Healthy adults	Alcohol related cognitive impairment	Korsakoff syndrome	
<i>n</i>	33	26	20	
Ages in years (<i>Mean ± SD</i>)	53.0 (6.7)	54.5 (8.1)	57.6 (8.7)	.122
Sex (% male)	15 (45.5)	20 (76.9)	15 (75.0)	.020
Level of education (<i>modus ± range</i>)	5 (3-6)	4 (1-6)	3 (2-6)	.010

Note. Education level was assessed using seven categories in accordance with the Dutch educational system. 1= 1-5 years of education; 2= 6 years of education; 3= 7-8 years of education; 4= 7-9 years of education; 5=7-10 years of education; 6= 7-16 years of education; 7= 17-20 years of education (Bouma et al., 2012).

Material

The Dutch version of the Montreal Cognitive Assessment (MoCA-D) is a cognitive screening instrument consisting of 13 short subtests, tapping the following cognitive functions: memory, visuospatial abilities, executive functions, attention and concentration, language, and orientation. Scores range from 0 to 30 and higher scores indicate better cognitive functioning. Administration takes approximately ten minutes. The short-term memory task involves two learning trials of five nouns and a delayed recall after approximately 5 minutes (5 points). Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Executive functions are assessed using an alternation task adapted from the Tail-Making Test B (1 point), a phonemic fluency task (1 point), and a verbal abstraction task (2 points). Attention, concentration and working memory are evaluated using a sustained attention task (1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). The subtest language consists of a three-item animal naming task (3 points) and repetition of two complex sentences (2 points). Finally, orientation to time and place is evaluated (6 points). The MoCA includes a correction for educational level by adding one point to the total MoCA score for people with less than 12 years of education (equaling an educational level of less than 5 in the Dutch educational system; Verhage 1964).

The Dutch version of the RBMT-3 was used (Wester et al., 2013) that is composed of 14 subtests belonging to six categories: verbal, visual, spatial, and prospective memory, orientation, and new learning. Remembering two names, and an immediate and delayed recall test of a story form the heart of the verbal memory subtask. Visual memory is assessed by face and picture recognition. Immediate and delayed recall of a route is used to measure spatial memory. Prospective memory involves remembering appointments, personal belongings, and shopping items. Spatial and temporal orientation is also evaluated. Finally, immediate and delayed recall task of a novel complex puzzle is assessed. Raw scores of each subtask were transformed into standard (scaled) scores in accordance with the original test manual (Wilson et al., 2008), taking into account the age of the participant. Afterwards the sum of the scaled scores is converted into a general memory index score (GMI), which has a mean of 100 and a standard deviation of 15. In this investigation GMI is used as a memory measure and higher scores indicate better memory functioning.

The English version of the RBMT-3 has a good construct validity, ecological validity and clinical validity. Wilson and colleagues (2008) provide strong evidence to support that the assessment is sensitive to memory problems. The Dutch version used in this study proves to have good sensitivity and adequate specificity (Wester et al., 2013a). Moreover, this version is a substantial

improvement over the original RBMT, as it reduces the problem of ceiling and floor effects and the number of misclassifications (Wester et al., 2013b).

Procedure

Data of the patients were collected from an existing clinical research data base of the Vincent Van Gogh Institute for Mental Health. Only patients were selected that had completed both the MoCA-D and the RBMT-3. The MoCA-D was administered to the two patient groups at intake by a trained neuropsychologist. Approximately six to eight weeks after admission to the Korsakoff Clinic, the RBMT-3 was administered by a neuropsychology intern during the course of an extensive neuropsychological assessment. The time interval between administration of the MoCA-D and the RBMT-3 was at most three months. The first version of the RBMT-3 was used for Korsakoff patients as well as for patients with cognitive impairment. Results of the MoCA-D were not used for establishing the multidisciplinary diagnosis, thus avoiding the problem of circularity.

The healthy participants were recruited from the personal network of the researchers. Only adults between 40 and 70 years of age and with lower than academic education were invited, in order to match the control group comparable with the patients. If the participants gave consent for participation, an appointment was made for the administration of the tasks. The assessment took place in a quiet room, in order to prevent distraction by environmental stimuli. First they were asked to provide some demographic information. After this the MoCA-D and the RBMT-3 were administered. The duration of the complete assessment was 45 to 60 minutes.

Analysis

To compare the MoCA Total score, MoCA Domain scores, and the RBMT-3 GMI score across the three groups, MANCOVA was performed. Educational level was included as covariate, since the three groups showed slight, yet significant differences on this demographic variable (see Table 1). Significant differences were further analyzed with Bonferroni-corrected post-hoc tests. ROC analyses were used to examine whether the MoCA differentiates between healthy controls and two patient groups.

To investigate the second question, i.e., the predictive value of the MoCA in relation to the severity of the memory impairment, all participants were divided into three groups based on their RBMT-3 GMI scores. Subjects with severe memory impairment, determined by a GMI score of at least two standard deviations below the UK normative mean ($GMI < 70$), were placed in the first group. People with mild memory deficits ($GMI 70 - 84$) were assigned to the second group and participants with unimpaired memory functioning to the

third group ($GMI \geq 85$). Subsequently, three ROC analyses were performed to examine the test's sensitivity and specificity. For all performed ROC analyses, optimal cut-off scores were defined as those with a sensitivity $\geq 80\%$ and a specificity $\geq 60\%$ (Blake et al., 2002). In case these criteria were not met, the best possible cut-off scores were reported instead.

Results

Table 2 shows the results of the MoCA Total and Domain scores, as well as the RBMT-3 GMI scores for all groups. On the overall measures, significant group effects were found for both the MoCA Total score ($F(2,75) = 30.37, p < .001$) and the RBMT-3 GMI score ($F(2,75) = 52.00, p < .001$). These effects were influenced positively by educational level ($F(1,75) = 17.30, p < .001$ and $F(1,75) = 6.18, p < .001$, respectively). Post-hoc analyses showed that the healthy participants had the highest performance and KS patients performed worse compared to the other groups.

Examination of the MoCA subdomains reveals that only the scores on the subdomain Memory significantly differed between the three groups ($F(2,75) = 33.04, p < .001$) with healthy people scoring highest and KS patients scoring lowest. On the subdomain Executive functioning healthy controls performed significantly higher than the two patient groups ($F(2,75) = 3.23, p < .05$), whereas the latter two performed at an equal level. Only the patients with cognitive impairment obtained a significantly lower score than the healthy controls ($F(2,75) = 7.39, p < .01$) on the visuospatial tasks. On the subtask Orientation, KS patients scored significantly lower than the two other groups ($F(2,75) = 32.81, p < .001$). Finally, on the two remaining subdomains (Attention and Language), no significant differences were found between the groups ($p = .08$ and $p = .43$, respectively).

Figure 1 shows the ROC curves of the MoCA detecting the three groups of participants. Table 3 displays an overview of the corresponding cut-off scores. The MoCA Total score significantly differentiated between KS patients and healthy controls ($AUC = .97, p < .001$). An optimal cut-off score of 23 was found (≤ 23 as indicator for KS) with a sensitivity of 88% and a specificity of 95%. Also, MoCA Total score could significantly distinguish patients with cognitive impairment from healthy controls ($AUC = .85, p < .001$). Here, an optimal cut-off score of 24 was detected with a sensitivity of 85% and a specificity of 69% (≤ 24 as indicator for cognitive impairment). For the distinction between the two patient groups, however, no optimal cut-off score could be determined ($AUC = .73, p < .01$). The best possible cut-off score was 20 (≤ 20 as indicator for KS) with a sensitivity of 73% and a specificity of 75%.

Table 2 Mean and standard deviations of MoCA-D Total score and Domain scores, and RBMT-3 General Memory Index (GMI) score per group.

	Group		Korsakoff syndrome (n = 20)	F-value	p-value
	Healthy adults (n = 33)	Alcohol related cognitive impairment (n = 26)			
MoCA-D Mean score (SD)					
Total score	26.52 (2.0)	22.04 (3.8)###	18.85 (3.7)####	30.37	< .001
Memory	3.33 (1.0)	2.04 (1.4)###	0.40 (0.8)####	33.04	< .001
Executive functioning	2.55 (0.8)	1.88 (1.1)#	1.75 (1.1)#	3.23	< .05
Attention and concentration	5.85 (0.4)	5.08 (1.3)	5.05 (1.5)	2.59	.08
Language	4.61 (0.7)	4.19 (0.8)	4.25 (0.8)	0.85	.43
Visuospatial abilities	3.61 (0.7)	2.54 (1.1)###	2.95 (9.1)	7.39	< .01
Orientation	5.76 (0.4)	5.42 (0.8)	3.60 (1.5)####	32.81	< .001
RBMT-3 Mean score (SD)					
GMI	91.64 (10.5)	78.46 (11.8)###	60.25 (4.4)####	52.00	< .001

Note. Significant difference with healthy adults: *p < .05, **p < .01, ***p < .001. Significant difference with alcohol-related cognitive impairment patients: *p < .05, **p < .01, ***p < .001.

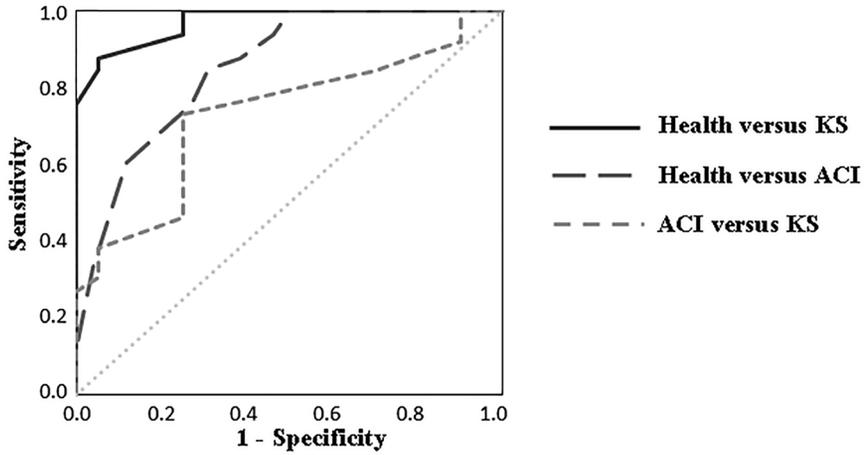


Figure 1 MoCA-D ROC curves for distinguishing Korsakoff syndrome from alcohol related cognitive impairment

Table 3 Sensitivity and specificity of the MoCA-D for the detection of Korsakoff (KS) and Alcohol related cognitive impairment (ACI).

MoCA-D Cut-off scores	Healthy versus KS		Healthy versus ACI		ACI versus KS	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
18					0.81	0.45
19					0.77	0.60
20					0.73 [#]	0.75 [#]
21	1.00	0.75			0.50	0.75
22	0.94	0.75	0.94	0.54	0.46	0.75
23	0.88 [*]	0.95 [*]	0.88	0.61		
24	0.85	0.95	0.85 [*]	0.69 [*]		
25	0.76	1.00	0.76	0.73		
26			0.61	0.88		

Note. ^{*}Optimal cut-off score; [#]best possible cut-off score.

Figure 2 shows the ROC-curves of the MoCA for the detection of the three GMI groups. The corresponding cut-off scores are shown in Table 4. Again, MoCA Total score can discriminate individuals with severe memory impairment from those without memory impairment ($AUC = .96, p < .001$) as well as individuals with mild memory deficits from those without memory impairment ($AUC = .82, p < .001$). For the first comparison, an optimal cut-off score of 23 was found (≤ 23 as indicator for a severe memory impairment; with a sensitivity of 91% and a specificity of 88%) and for the second comparison, an optimal cut-off score of 24 could be established (≤ 24 as indicator for mild cognitive impairment) with a sensitivity of 88% and a specificity of 71%. Finally, individuals with severe and mild memory impairment could also be differentiated ($AUC = .75, p < .01$). A sensitivity of 81% and a specificity of 69% was found in conjunction with an optimal cut-off score of 20 (≤ 20 as indicator of severe memory impairment).

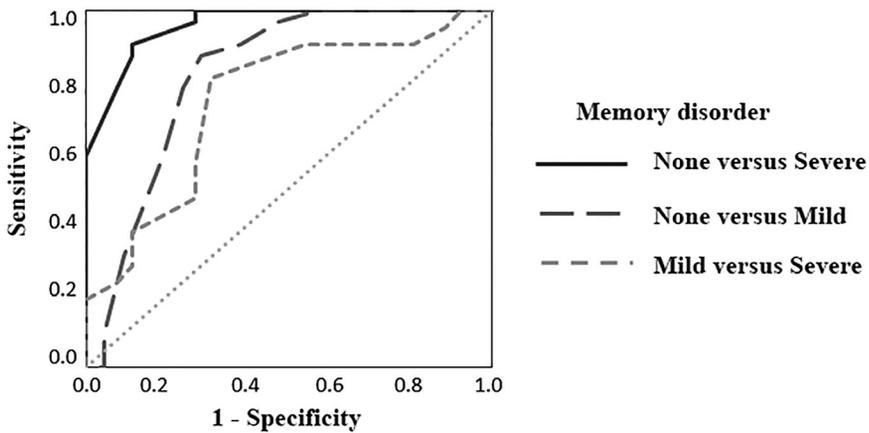


Figure 2 MoCA-D ROC curves for distinguishing mild from severe memory disorders

Table 4 Sensitivity and specificity of the MoCA-D for the detection of mild and severe memory disorders

MoCA-D Cut-off scores	None versus Severe		None versus Mild		Mild versus Severe	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
18					0.91	0.46
19					0.86	0.58
20					0.81*	0.69*
21	1.00	0.73			0.57	0.73
22	0.97	0.73	0.97	0.52	0.48	0.73
23	0.91*	0.88*	0.91	0.62		
24	0.78	0.88	0.88*	0.71*		
25	0.78	0.92	0.78	0.76		
26			0.59	0.81		

Note. *Optimal cut-off score.

Discussion

This is the first study that examines predictive and convergent validity of the MoCA in a combined sample of KS patients, patients with alcohol-related cognitive impairment not fulfilling the criteria for KS, and healthy individuals. The MoCA was able to distinguish between these three diagnostic classification groups, and also between subgroups based on three levels of memory impairment based on the RBMT-3 GMI score. These findings are in agreement with previous studies showing that (everyday) memory is more affected in Korsakoff patients than in the patient group with cognitive impairment, compared to healthy controls. The MoCA memory score was the only subdomain on which all three groups differed significantly.

Main aim of this study was to examine the diagnostic accuracy of the MoCA. Previous research already showed that the MoCA is able to differentiate MCI and Alzheimer dementia from healthy controls (Freitas et al., 2013; Fujiwara et al., 2010; Lee et al., 2008; Luis et al., 2009; Nasreddine et al., 2005). Furthermore, the MoCA is able to classify cognitive dysfunction in patients with substance dependence (Copersino et al., 2009). These results coincide with findings of the present study that showed the MoCATotal score to be able to distinguish chronic alcoholics with cognitive impairment (non-KS) from healthy controls, with an

optimal cut-off score (≤ 24) that had adequate sensitivity and specificity. The same was true for KS patients (cut-off score of ≤ 23).

Although the MoCA appears to have adequate diagnostic accuracy in the present sample, a note of caution should be mentioned here. While the MoCA is able to classify the two patient groups compared to controls, the discriminatory power of the MoCA seems to be moderate when comparing the two patient groups directly. The best possible cut-off score for distinguishing these two groups (≤ 20) had a sensitivity and specificity of 73% and 75%, respectively, indicating that about 27% of the KS patients is classified as a non-KS patient whereas, and 25% of the non-KS patients is classified as having KS. Based on these findings, extensive neuropsychological assessment may have an added value to determinate the adequate diagnosis (KS vs. Alcohol-related cognitive impairment). For the prediction of memory impairment severity by means of the MoCA, promising results were found. The MoCA is able to distinguish between people with no, mild or severe cognitive impairment, with good sensitivity and specificity. Unlike most previous studies, the present research also compared the mildly and severely memory-impaired groups directly, showing a high discriminatory power of the MoCA for these two patient groups.

The question arises how these findings translate into clinical practice. Given the emergence of optimal cut-off scores, the MoCA is able to predict the severity of memory impairment in a sample of cognitively impaired patients with alcohol-use disorder. Still, in cases with MoCA scores between 20 and 24, it is more difficult to adequately classify memory impairment severity since in this score interval, both severe memory impairment and mild memory impairment are included. In other words, a score in this range signals that a memory impairment is present, but cannot differentiate its severity, requiring more extensive neuropsychological memory testing.

Several limitations of this study have to be mentioned. First, in both patient groups, the MoCA was administered during admission to the clinic. For the majority of patients, alcohol abstinence could not be guaranteed at that point in time. Some studies report that cognitive impairments in alcoholics persist after a short period of abstinence (Block et al., 2002; Munro et al., 2000). However, others suggest that some recovery of cognitive functioning is possible after a period of abstinence (Bates et al., 2005; Oscar-Berman et al., 2004; Walvoort et al., 2013). Taking into account that the RBMT-3 was administered after a period of abstinence (i.e., more than 6 weeks after admission), it is possible that the two patient groups scored lower on the MoCA when compared with scoring levels on the RBMT-3. Moreover, a slight difference in educational level was detected in the three groups. Bearing in mind that educational level has a positive influence on cognitive abilities (Acevedo et al., 2007; Ganguli et al., 2010), the elevated

scores of the healthy controls could be partially explained by their higher educational level, although inclusion of education level as a covariate still resulted in significant between-group differences. Finally, this specific study investigated only to what extent the MoCA is able to predict the severity of memory impairment. Future research will have to address the validity claim for other cognitive domains.

In sum, results from the present study suggests that the MoCA has discriminatory power in the diagnosis of patients with alcohol-related cognitive impairments and predictive capacities with regard to the severity of memory impairment. While it can be concluded that the MoCA is a useful screening instrument, it should be stressed that it cannot substitute a more extensive neuropsychological assessment, as this also covers other cognitive domains and uses validated tests for the assessment of specific sub-processes within a domain (e.g., is able to differentiate memory encoding from retrieval). The latter is often essential for establishing a detailed analysis of the cognitive profile, which in turn is vital for adequate treatment selection, especially in relation to interventions using cognitive rehabilitation principles.

Acknowledgements

The authors report no conflicts of interest in this work. The MoCA-D is available for free from www.mocatest.org. We thank Pearson Assessment B.V., Amsterdam, The Netherlands, for providing the RBMT-3 test materials and for authorizing the Dutch translation.

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CHAPTER

Summary and discussion



CHAPTER 9

Summary

The present thesis examined the applicability of the Rivermead Behavioural Memory Test (RBMT) in alcohol-related cognitive disorders. The performance of patients with Korsakoff's syndrome on the original RBMT was examined, and the performance on the original RBMT was compared with a widely used word-list learning test, the Dutch version of the California Verbal Learning Test (CVLT), to establish the discriminative power of both memory tests in distinguishing between different patient groups with alcohol-related cognitive impairment. Also, the psychometric properties of the Dutch version of the Rivermead Behavioural Memory Test-Third Edition (RBMT-3) were examined. Furthermore, it was studied whether this version was an improvement over the original RBMT, and the applicability of the RBMT-3 and the Montreal Cognitive Assessment in patients with alcohol-related cognitive disorders was examined.

In *Chapter 2*, a general description of the cognitive consequences of long-term alcohol use was presented. Prolonged alcohol use may cause damage to the brain, potentially producing cognitive deficits that may range from mild to an alcohol-related dementia (ARD). In combination with malnutrition, resulting in thiamine deficiency, Korsakoff's syndrome may be the result as well. This syndrome is characterized by severe amnesia, especially anterograde amnesia, and executive dysfunction. In clinical practice, delineating cognitive deficits resulting from alcohol use, Korsakoff's syndrome or alcohol-related dementia may be difficult, as for all these conditions clear biomarkers are to date lacking. Moreover, the abnormalities in the brain supposed to underlie Korsakoff's syndrome cannot be easily detected by conventional brain imaging techniques. Lastly, alcohol-related dementia is a syndromal diagnosis without a discrete neuroanatomical substrate. Also, consensus on the clinical criteria of the discussed syndromes is changing.

The original Rivermead Behavioural Memory Test (RBMT) and its use in the clinical practice of the neuropsychological examination of patients with Korsakoff's syndrome was the focus of *Chapter 3*. The RBMT assesses memory problems in an everyday context. Results on the RBMT are presented that were obtained in a large sample of diagnosed Korsakoff patients. In the standard scoring procedures used in the RBMT, much of the information about performance on individual items is lost. Exactly this information is important in clinical practice to be able to assess the patient's strengths and weaknesses and to tailor subsequent treatment. For this reason not only quantitative analysis was performed, but also a qualitative analysis of the RBMT subtest profile in KS patients was provided. The data presented here may serve as a frame of reference in the assessment of individuals with alcohol-related memory problems or deficits.

In *Chapter 4*, the performance of patients with Korsakoff's syndrome, alcohol dependent patients with cognitive deficits, and alcohol dependent patients without cognitive dysfunctions, was compared on the original RBMT versus the CVLT. As might be expected, Korsakoff patients were significantly more impaired on all RBMT subtests and CVLT measures compared with the cognitively impaired non-Korsakoff alcoholics. However, in agreement with previous findings that the RBMT is not sensitive for identifying subtle memory deficits (Lezak et al., 2012), no differences were found between the alcoholics without cognitive deficits and the non-Korsakoff alcoholics with cognitive impairments on the RBMT, except on one subtest. In contrast, the RBMT was able to discriminate moderate from severe memory dysfunctions. All subtests differed significantly between Korsakoff and cognitively impaired alcoholics. Comparing the alcoholic controls with the cognitively impaired alcoholics using the CVLT as measure of memory performance, alcoholic patients without signs of cognitive impairment showed a significantly lower speed of forgetting, and a better performance on the short-term and long-term free recall measures. Memory performance in Korsakoff patients on the CVLT was higher when patients were given cues (either on a cued recall or recognition trial). Still, their performance was lower than the alcoholic patients without signs of cognitive impairment and cognitively impaired alcoholics. The alcoholic patients without signs of cognitive impairment obtained unimpaired scores on cued recall and recognition tests. By means of discriminant function analysis of the subtests, measures of free and cued recall of the CVLT were able to discriminate better between the three patient groups than recognition performance. The immediate and delayed versions of the Story Recall RBMT subtest added to the discrimination of the groups. It can be hypothesized that the contextual aspect of the Story Recall subtest, in combination with the potentially larger motivational and attentional demands of this test compared to other RBMT and CVLT subtests, may explain this result. Cognitively impaired alcoholics and alcoholics without cognitive impairments did not differ on the story recall subtest. Receiver-operating characteristics analyses showed that the total standardized profile score of the RBMT and the total score of the CVLT significantly discriminated Korsakoff from cognitively impaired patients, but not cognitively impaired from unimpaired alcoholics. This once more underlines the relative insensitivity of the RBMT for more subtle memory deficits.

In *Chapter 5* memory performance of 141 healthy adults was recorded and used to examine the psychometric properties of the Dutch version of the RBMT-3. This new version showed moderate reliability (internal consistency). Exclusion of the subtests 'Belongings', 'Appointments', 'Picture Recognition' and 'Novel Task-immediate recall' increased the reliability coefficient. The RBMT-3 proved

to have solid construct validity. Using principal component analysis, we were able to subtract one general factor, i.e., the Memory Index, with all subtests having a positive loading on this factor. The combined results suggest that the RBMT-3 subtests measure a single underlying memory construct. Overall, our findings are consistent with the findings that Wilson and colleagues (2008) reported in their UK sample. Intraclass correlation analysis on the two parallel versions of the RBMT-3 was indicative for good test-retest reliability. Test scores were correlated with age and verbal intelligence, but no sex differences were found.

Chapter 6 describes a study that examines whether the RBMT-3 is an improvement over the original RBMT in a heterogeneous sample of patients with alcohol-related memory disorders and healthy participants. With respect to ceiling and floor effects, the RBMT-3 is a substantial improvement over the original RBMT. The increase in the number of items in several subtests of the RBMT-3 has resulted in less participants performing at or near the subtest's ceiling and also resulted in less floor level performances. Moreover, the RBMT-3 classifies less healthy participants as impaired, which was a problem in the original RBMT.

Aim of the study presented in *Chapter 7* was to examine whether the RBMT-3 can be used to demonstrate alcohol-related deficits, and whether more subtle alcohol-related deficits can be distinguished from those of patients with Korsakoff's syndrome, and from healthy controls. Results show that both patients with Korsakoff syndrome and non-Korsakoff alcoholics with cognitive deficits perform worse than matched non-alcoholic controls. Largest effect sizes were found on tests of delayed recall, orientation, as well as cued and uncued prospective memory in the Korsakoff patients. With respect to the non-Korsakoff alcoholics, effect sizes were smaller compared to the healthy controls than in the Korsakoff group. On the subtests 'Orientation', 'Memory for Pictures', 'Messages' and 'Prose Recall', performance was at control level. Korsakoff patients performed worse than the non-Korsakoff group on all subtests except 'Story Recall-Immediate'. The effect sizes of the non-Korsakoff patient group were in the moderate to large range, and although the memory deficits were not as severe as in Korsakoff patients, they are clinically relevant and may hamper everyday functioning.

Finally, *Chapter 8* describes the study on the discriminatory power of a cognitive screen, the Montreal Cognitive Assessment (MoCA), to distinguish between mild and severe forms of memory impairment, such as Korsakoff patients, chronic alcoholics with cognitive deficits and healthy non-alcoholic controls. With good sensitivity and specificity, the MoCA was able to distinguish between these diagnostic categories, and also between subgroups based on

three levels of memory impairment based on the scores of the RBMT-3 General Memory Index. The MoCA memory score was the only subdomain on which all three groups differed significantly. For all comparisons between the patient categories, specific cut-off scores were established.

Discussion

The aim of this thesis is to examine the applicability, reliability and validity of the RBMT in the assessment of patients with mild, moderate or severe memory deficits due to alcohol-use disorder. Here, some of the strengths and limitations will be discussed, and recommendations for future studies and clinical practice are proposed.

The RBMT-3 has been developed in response to some problems of earlier versions of the RBMT. That is, some subtests in earlier versions of the RBMT appeared to be too difficult (RBMT-E) or too easy (RBMT[-II]) for some patients. Although the UK version of the RBMT-3 was already published in 2008, to our knowledge, no empirical studies using the RBMT-3 have been performed and published to date. In the present studies, the Dutch translated and adapted RBMT-3 showed to be an improvement over the original RBMT as it demonstrated to have good psychometric properties, and discriminative power to distinguish patients with Korsakoff's syndrome, non-Korsakoff alcoholic patients with cognitive disorders and healthy non-alcoholic controls. Also, the newly added subtest (Novel Task) is a procedural learning task which intended to measure a person's ability to acquire a new procedural task, a competence that is crucial for everyday functioning.

In a comparison of the Dutch and UK norms of the original RBMT for persons under age 70, the standardised item scores of the Dutch sample appeared to be lower (Bouma, Mulder & Lindeboom, 2012). This discrepancy probably could be attributed to the selection procedure of the Dutch norm group of the RBMT, of which most participants attended a memory training course. As a result, the normative sample possibly included patients with early neurodegenerative disease (Van Balen & Groot Zwaaftink, 1993). The healthy controls who completed the RBMT-3 were screened for psychiatric and neurological disease, but it should be noted that the sample of healthy participants is still too small to calculate reliable normative data. The present findings on the healthy controls demonstrate that age has an effect on the Dutch RBMT-3. This is in accordance with the age effect reported by Wilson et al. (2008) in the UK sample.

Concerning the influence of intelligence, this study is the first to examine the influence of IQ on the RBMT-3, showing that IQ has a significant moderate effect

on the RBMT-3 test performance. However, the presented control data are derived from small homogeneous samples of relatively higher educated people. Adequate normative data should be more representative of the general population in terms of educational levels. Thus, more healthy participants from a wider range of educational backgrounds should be examined in order to produce reliable and clinically applicable normative data.

The RBMT-3 is the only clinically available memory test that was specifically designed to evaluate everyday memory functioning in order to provide relevant information for use in the diagnostic process, as well as for rehabilitation purposes. To examine the ecological validity of the RBMT-3, Wilson et al. (2008) administered the Prospective and Retrospective Memory Questionnaire (PRMQ), a rating scale for everyday memory problems with self- and proxy-rating versions, in a sample of patients and healthy participants. As expected, patients reported less memory problems than proxies, but only a moderate correlation was reported with the RBMT-3. In the present thesis, ecological (i.e., predictive) validity was not extensively examined.

A recommendation for future research is to relate the RBMT-3 performance to clinically relevant outcome measures. Memory rating scales such as the PRMQ may not be the optimal outcome measure, as discrepancies between objective and subjective measures of memory problems have been reported previously (see, e.g., Mol et al., 2006), which is even more problematic in cognitively impaired alcoholics who may also have a lack of insight into their cognitive problems. Possibly, outcome measures that assess the patient's everyday competency (for instance, the Patient Competency Rating Scale; Prigatano et al. 1990) may be better instruments to establish the RBMT-3's predictive validity. Also, more research is needed to examine the RBMT-3's concurrent validity, for example using other extensive neuropsychological memory test batteries, such as the Wechsler Memory Scale – Fourth Edition (WMS-IV).

From a clinical perspective, the RBMT-3 seems a valid addition to the existing neuropsychological tests available; it is a feasible test to administer even in patients with major neurocognitive disorder. However, it should be noted that studies in non-alcoholic patients with cognitive impairments using the RBMT-3 are still lacking. Other patient groups in which amnesia is a prominent characteristic, such as older people with Mild Cognitive Impairment or dementia, stroke patients, or patients with traumatic brain injury, should be examined using the RBMT-3. Also, the sensitivity of the parallel versions for detecting changes in performance, for instance before and after rehabilitation or other interventions, remains to be studied.

Moreover, one could argue that, by definition, memory deficits are a prominent characteristic to diagnose Korsakoff's syndrome and to distinguish

this syndrome from non-Korsakoff alcoholics. As a result, one could argue that *any* memory test is able to discriminate these patient groups (see also Chapter 8). However, it should be stressed that the diagnosis of Korsakoff's syndrome in the studies here presented was not only based on the memory test scores, but also on medical history, neuroradiological evidence and extensive (neuro) psychological assessment of the non-memory domains. Although the present studies focused on memory function to discriminate different diagnostic categories, it should be stressed that alcoholic patients may also show deficits in non-memory domains (see also Van Oort & Kessels, 2009; Walvoort, Wester & Egger, 2013) and that a clinical diagnosis should never be made on the basis of a single neuropsychological test.

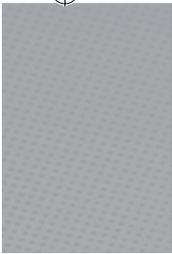
Conclusion

In this thesis, an overview was presented of the possible cognitive consequences in alcohol-use disorders, followed by empirical studies using the original RBMT and the recently developed Dutch version of the RBMT-3. For the first time, a number of studies are presented concerning the feasibility of the RBMT-3 in the assessment of alcohol-related cognitive disorders. An improvement over the original RBMT, the third edition seems to be a reliable, valid and useful clinical research tool for the assessment and treatment of patients with alcohol-related cognitive disorders.

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Nederlandse samenvatting
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Nederlandse samenvatting

Het gebruik van alcohol is verantwoordelijk voor het merendeel van de vragen om behandeling in de verslavingszorg. Bijna tachtig procent van de mensen die behandeling zoeken voor hun alcohol verslaving hebben dit al eerder gedaan. Een groot deel van hen heeft cognitieve problemen, variërend van subjectieve klachten die met cognitieve testen niet zijn te objectiveren, tot milde en zeer ernstige stoornissen, zoals die gezien worden bij het syndroom van Korsakov. Deze cognitieve problemen omvatten tekorten in het geheugen, de executieve functies, de visuo-spatiële vermogens, psychomotorische vaardigheden en het emotionele functioneren. Het wordt steeds duidelijker dat cognitieve achteruitgang bijdraagt aan een slecht behandelresultaat zoals terugval in alcohol-misbruik of ernstige beperkingen in het dagelijks leven. Het vaststellen van ernst en aard van de cognitieve stoornissen aan het begin van het behandeltraject middels een neuropsychologisch onderzoek is derhalve cruciaal.

Er is in de loop van de jaren met name veel onderzoek gedaan naar het geheugen-functioneren bij het syndroom van Korsakov. Relatief minder studies zijn gepubliceerd naar geheugenstoornissen bij alcoholafhankelijke personen zonder het syndroom van Korsakov. Vanuit klinisch perspectief maken de heterogeniteit en de graduele aard van alcohol-gerelateerde stoornissen het lastig om duidelijk onderscheid te kunnen maken tussen enerzijds chronisch alcoholisten met en zonder geheugen stoornissen, en mensen met het syndroom van Korsakov of alcoholgerelateerde dementie anderzijds.

Traditionele geheugentesten blijken in de praktijk minder geschikt om subjectieve geheugenklachten te objectiveren en problemen in het functioneren van het alledaagse geheugen vast te stellen. Ecologisch valide geheugentesten zijn daarom ontwikkeld om dit tekort van de klassieke testen te compenseren. Deze testen zijn er op gericht te bepalen of een patiënt al dan niet moeilijkheden heeft in voor het dagelijks leven relevante geheugentaken, waarbij de traditionele testen ons informatie kunnen verschaffen over welk geheugen systeem is aangetast.

Barbara Wilson en haar collegae ontwikkelden en publiceerden in 1985 de Rivermead Behavioural Memory Test, een ecologisch valide geheugen test, met als doel om bij mensen met hersenletsel in het dagelijks leven geheugenproblemen te kunnen objectiveren en voorspellen. Bovendien zou deze test kunnen dienen om veranderingen in het functioneren, bijvoorbeeld na behandeling, te kunnen volgen.

In dit proefschrift is de toepasbaarheid van de originele Rivermead Behavioural Memory Test (RBMT) onderzocht bij alcoholgerelateerde cognitieve stoornissen. Daarnaast beschrijft het de ontwikkeling van de Nederlandse versie van de

Rivermead Behavioural Memory Test-3 (RBMT-3). De psychometrische eigenschappen alsmede de toepasbaarheid van de RBMT-3 bij patiënten met stoornissen in het gebruik van alcohol zijn eveneens onderzocht.

In *Hoofdstuk 2* worden de cognitieve gevolgen van langdurig alcoholgebruik beschreven. Langdurig alcoholgebruik kan schade aan de hersenen veroorzaken, die kan leiden tot cognitieve defecten. Deze kunnen variëren van mild tot een alcoholgerelateerde dementie. In combinatie met thiaminedeficiëntie kan dit resulteren in het syndroom van Korsakov. Dit syndroom wordt gekenmerkt door ernstige anterograde amnesie en executieve functiestoornissen. In de klinische praktijk is het lastig om cognitieve defecten door alcoholgebruik, het syndroom van Korsakov of alcoholgerelateerde dementie van elkaar af te bakenen, omdat voor deze aandoeningen duidelijke biomarkers vooralsnog ontbreken. Bovendien zijn de hersenafwijkingen die verondersteld worden ten grondslag te liggen aan het syndroom van Korsakov niet makkelijk vast te stellen met conventionele beeldvormende technieken. Tenslotte is alcoholgerelateerde dementie een syndromale diagnose zonder een duidelijk neuro-anatomisch substraat. De consensus ten aanzien van de klinische criteria van de genoemde syndromen is nog steeds aan verandering onderhevig.

De originele RBMT en het gebruik ervan bij neuropsychologisch onderzoek van patiënten met het syndroom van Korsakov is de focus van *Hoofdstuk 3*. De RBMT meet geheugenproblemen in een alledaagse context. De resultaten op de RBMT die zijn verzameld bij een grote steekproef gediagnosticeerde korsakovpatiënten worden gepresenteerd. Bij de standaard scoringsprocedure van de RBMT, gaat veel informatie over de prestaties op afzonderlijke test items verloren. Omdat juist deze informatie van belang is om de sterkten en zwakheden van de patiënt te meten, en op basis hiervan een behandelplan op te stellen, is naast een kwantitatieve analyse ook een kwalitatieve analyse van de subtest profielen uitgevoerd. De gepresenteerde data kunnen dienen als referentiekader in het onderzoek van mensen met alcoholgerelateerde geheugenproblemen of defecten.

In *Hoofdstuk 4* worden de prestaties van patiënten met het syndroom van Korsakov, alcoholafhankelijke patiënten met cognitieve defecten, en alcoholafhankelijke patiënten zonder cognitieve disfuncties, met elkaar vergeleken op de originele RBMT versus de Verbale Leer- en Geheugen Test (VLGT). Zoals te verwachten waren de korsakovpatiënten significant meer gestoord op alle RBMT-subtesten en de VLGT-maten, vergeleken met cognitief gestoorde alcoholisten zonder Korsakov. Op de RBMT werden tussen de alcoholisten met en zonder cognitieve stoornissen, met uitzondering van één subtest, geen verschillen gevonden. Dit is een bevestiging van eerder onderzoek dat aantoonde dat de RBMT niet sensitief genoeg is om subtiele geheugendefecten vast te

stellen. Een vergelijking van deze twee groepen met de VLGT als geheugenmaat liet zien dat alcoholisten zonder cognitieve achteruitgang een lagere vergeet-snelheid hadden, en beter presteerden op de kortetermijn- en langetermijn-vrije- herinneringsmaten. Als korsakovpatiënten bij de VLGT hints kregen, verbeterde dit hun prestaties. Door middel van discriminantanalyse van de subtesten konden de vrije- en cued-recall-maten van de VLGT een beter onderscheid maken tussen de drie patiënten groepen dan de prestatie op de her-kenningsmaat. De onmiddellijke en uitgestelde versies van de RBMT-subtest 'Verhaal' droegen eveneens bij aan het onderscheiden van de twee groepen. Mogelijk wordt dit resultaat verklaard door het contextuele aspect van deze subtest, gecombineerd met de potentieel grotere eisen ten aanzien van motivatie en aandacht ervan in vergelijking met andere RBMT- en VLGT-subtesten. Voorts toonden analyses aan dat de totale standaard-profielscore van de RBMT en de totale score van de VLGT, significant onderscheid maakten tussen korsakov-patiënten en cognitief gestoorde alcoholisten, maar niet tussen cognitief gestoorde en cognitief ongestoorde alcoholisten. Dit kan gezien worden als een bevestiging van de relatieve ongevoeligheid van de RBMT voor subtiele geheugendefecten.

In *Hoofdstuk 5* werden de psychometrische eigenschappen van de Nederlandse versie van de RBMT-3 onderzocht. Deze nieuwe versie liet een redelijke interne consistentie zien. Exclusie van de subtesten 'Persoonlijke Bezittingen', 'Afspraken', 'Herkennen van Plaatjes' en 'Niet-alledaagse Taak – Onmiddellijke Reproductie' vergrootten de betrouwbaarheids-coëfficiënt. De RBMT-3 heeft een solide constructvaliditeit. Op een principale-componenten-analyse bleken alle subtesten positief te laden op een algemene factor, de Geheugen Index. De gecombineerde resultaten suggereren dat de RBMT-3-subtesten één enkel onderliggend geheugenconstruct meten. Globaal komen deze bevindingen overeen met de door Wilson en collegae gerapporteerde resultaten in de Engelse populatie. Intra-class-correlatie-analyse van de twee parallelversies van de RBMT-3 wees op een goede test-hertestbetrouwbaarheid. Testscores correleerden met leeftijd en verbale intelligentie maar er werden geen sekse verschillen aangetoond.

Hoofdstuk 6 beschrijft een studie waarin onderzocht is of de RBMT-3 een verbetering is ten opzichte van de originele RBMT in een heterogene patiëntenpopulatie met alcoholgerelateerde geheugenstoornissen en gezonde proefpersonen. Met betrekking tot plafond- en bodem-effecten, is de RBMT-3 een substantiële vooruitgang. Het grotere aantal items in de verscheidene subtesten van de RBMT-3 resulteerde in minder proefpersonen die op of bijna op plafondniveau van de subtesten presteerden, en zorgde ook voor minder prestaties op bodemniveau. Bovendien classificeerde de RBMT-3 minder gezonde personen als geheugen gestoord, wat bij de originele RBMT een probleem was.

Het doel van de in *Hoofdstuk 7* gepresenteerde studie was om te onderzoeken of de RBMT-3 gebruikt kan worden om alcoholgerelateerde geheugendefecten aan te tonen, en of subtielere alcoholgerelateerde tekorten onderscheiden kunnen worden van die van patiënten met het syndroom van Korsakov, en van gezonde controles. De resultaten laten zien dat zowel patiënten met het syndroom van Korsakov als alcoholisten zonder Korsakov maar wel met cognitieve stoornissen, slechter presteren dan vergelijkbare niet-alcoholische controlepersonen. De sterkste effect groottes werden gevonden op de testen met uitgestelde reproductie, oriëntatie, alsmede op het prospectieve geheugen, met en zonder hints, bij de korsakovpatiënten. Met betrekking tot de alcoholisten zonder Korsakov, waren de effect groottes kleiner vergeleken met de gezonde controles dan in de korsakovgroep. Op de subtesten 'Oriëntatie', Herkennen van Plaatjes', 'Boodschappen' en 'Verhaal Onthouden', lag de prestatie op het niveau van de gezonde vrijwilligers. Korsakovpatiënten presteerden slechter dan de niet-Korsakovgroep op alle subtesten behalve de onmiddellijke reproductie van het 'Verhaal'. De effect groottes van de niet-korsakovgroep waren matig tot groot, en hoewel de geheugendefecten niet zo ernstig waren als bij korsakovpatiënten, waren ze klinisch relevant en vormden een mogelijke beperking in het dagelijks functioneren.

Tenslotte beschrijft *Hoofdstuk 8* een onderzoek naar het discriminerend vermogen van een cognitieve screeningstest, de Montreal Cognitive Assessment (MoCA), in het onderscheiden van milde en ernstige vormen van geheugenverlies, zoals bij korsakovpatiënten, chronisch alcoholisten met cognitieve tekorten en gezonde niet-alcoholistische controles. De MoCA kon met een goede sensitiviteit en specificiteit deze diagnostische categorieën onderscheiden, en ook onderscheid maken tussen subgroepen gebaseerd op de drie niveaus van geheugenachteruitgang gebaseerd op de Algemene Geheugen Index van de RBMT-3. De MoCA-geheugen score was het enige subdomein waarop alle drie groepen significant verschilden. Voor alle vergelijkingen tussen de patiëntcategorieën, werden specifieke cut-off scores berekend.

Tot besluit

De RBMT-3 werd ontwikkeld om een aantal problemen uit eerdere versies van de RBMT op te lossen. Zo bleken sommige subtesten van de Rivermead Behavioural Memory Test-Extended (RBMT-E) te moeilijk of te makkelijk (RBMT-II) voor een aantal patiënten. Zowel de RBMT-E als de RBMT-II zijn echter nooit in een Nederlandstalige versie uitgebracht. Uit de in dit proefschrift gepresenteerde studies kan de Nederlandstalige versie van de RBMT-3

beschouwd worden als een verbetering van de originele RBMT. De gegevens die bij de gezonde vrijwilligers verzameld zijn, kunnen gebruikt worden om normgegevens te ontwikkelen voor de RBMT-3, zodat deze ook in de klinische praktijk gebruikt kan worden.

Als verbetering van de originele RBMT lijkt de RBMT-3 een betrouwbaar, valide en nuttig klinisch instrumentarium te zijn in de diagnostiek en behandeling van patiënten met alcoholgerelateerde cognitieve stoornissen. De RBMT-3 is voor zover bekend de enige ecologisch valide testbatterij voor het geheugen. Het zou interessant zijn om in vervolgonderzoek de RBMT-3 te vergelijken met andere geheugenbatterijen, zoals de Wechsler Memory Scale-IV. Ander onderzoek zou zich kunnen richten op de relatie van de RBMT-3 tot uitkomstmaten van het dagelijks functioneren zoals gemeten met de Patient Competency Rating Scale (Prigatano).



Dankwoord

En dan is het af, het proefschrift. Sneller dan ik had gedacht en gehoopt. Het promotie-onderzoek moest af om de Topklinische erkenning voor de Korsakov Kliniek te kunnen halen. Zo was het afgesproken toen Toon Wijdeveld, toenmalig medisch manager van de divisie verslavingszorg van het Vincent van Gogh mij eind 2009 vroeg of ik niet wilde promoveren om die erkenning te kunnen verwerven. Menigmaal heb ik in de afgelopen jaren spijt gehad van mijn toezegging. Maar ik wilde het Topklinische keurmerk zelf ook zo graag. Alle moeite is niet voor niets geweest, want eind december 2013 heeft de Korsakov Kliniek daadwerkelijk het predicaat gekregen en mag zich nu Topklinisch Centrum noemen.

In mijn dankwoord moet ik beginnen met degene die mij zover heeft gekregen om aan het traject te beginnen, dat uiteindelijk heeft geleid tot dit proefschrift: Harry van Donzel. Bijna zestien jaar hebben we samen gewerkt om de Korsakov Kliniek te krijgen, waar deze nu is. Op de moeilijke momenten dat ik op het punt stond het bijtje erbij neer te gooien, wist je me toch weer te motiveren met je optimisme. Helaas heb je de laatste fase van het Topklinisch traject net niet meer als leidinggevende van de kliniek kunnen meemaken. Als paranimf echter sta je me tot het laatste moment nog bij. Harry, hartelijk bedankt!

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Curriculum Vitae

Arie Wester was born on July 16th 1951 in Venray, the Netherlands. In 1970 he completed his secondary school education (Gymnasium A) at the Boschveldcollege in Venray, and studied psychology at Radboud University Nijmegen in the same year, majoring in Clinical Psychology. Meanwhile, he graduated as social studies teacher in 1980. In 1981, he obtained his master's degree. His master thesis examined the influence of specific and non-specific variables in behavior therapy. He then started as teacher of psychology at in-service nursing education centre Den Hoebert in Venray, until 1993. In 1984 he started as psychologist in Psychiatric Centre Venray (now Vincent van Gogh Institute for Psychiatry). Since 1989 he is involved in the Korsakoff Clinic; initially as neuropsychologist, and since 1992 as head. In 1999 he obtained his registration as certified health-care psychologist. In 2010 he was registered as certified clinical neuropsychologist. This same year he started working on his PhD project. Since 2010 he is responsible for the postgraduate program 'Neuropsychological Assessment' of the postgraduate specialist program in clinical psychology at the RINO, Utrecht. Under his direction as figurehead and as senior investigator, the Korsakoff Clinic received the Centre of Excellence certification in 2013.

Arie Wester werd op 16 juli 1951 geboren in Venray. In 1970 behaalde hij het Gymnasium-A diploma aan het Boschveldcollege in Venray en ging in hetzelfde jaar psychologie studeren aan de Radboud Universiteit in Nijmegen. Na in 1980 aan de universiteit zijn eerste graads bevoegdheid voor maatschappijleer te hebben gehaald, studeerde hij in 1981 af in de klinische psychologie. Zijn doctoraal-scriptie ging over de invloed van specifieke en niet-specifieke factoren in gedragstherapie. Kort daarna startte hij als docent psychologie aan de inservice opleidingen voor psychiatrisch verpleegkundigen en ziekenverzorgenden, Den Hoebert in Venray, tot 1993. In 1984 begon hij als psycholoog in het Psychiatrisch Centrum Venray (nu Vincent van Gogh voor geestelijke gezondheid). Sinds de start van de Korsakov Kliniek in 1989 is hij bij de afdeling betrokken; aanvankelijk als neuropsycholoog en vanaf 1992 als hoofd (programmameider/programma-manager). In 1999 werd hij geregistreerd als Gz-psycholoog. In de periode van 2001 tot 2001 werkte hij op detacheringsbasis part-time als neuropsycholoog bij de korsakovafdeling van de Gelderse Roos in Wolfheze. In 2010 behaalde hij zijn registratie tot klinisch neuropsycholoog. In hetzelfde jaar is hij begonnen met het promotieonderzoek dat in dit proefschrift wordt beschreven. Sinds 2010 is hij als hoofddocent verantwoordelijk voor het blok Neuropsychologische Diagnostiek van de postdoctorale opleiding klinische psychologie van RINO Groep te Utrecht. Vanaf 2012 is hij als praktijkopleider van de postdoctorale

CURRICULUM VITAE

opleiding tot klinisch neuropsycholoog werkzaam bij de afdeling Thalamus van Pro Persona in Wolfheze; en recent is hij praktijkopleider voor de postdoctorale opleiding tot gz-psycholoog (RINO Zuid) in Vincent van Gogh. In december 2013 behaalde de Korsakov Kliniek onder zijn leiding als boegbeeld en senior onderzoeker het TOPGGz keurmerk.

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