Reconstructing cognition in Korsakoff's syndrome

Diagnosis, residual capacities, and rehabilitation

Het reconstrueren van cognitie in het syndroom van Korsakov

Diagnose, restcapaciteiten en revalidatie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 8 januari 2016 des middags te 2.30 uur

door
Freerk Abel Oudman

geboren op 3 november 1985

te Amersfoort

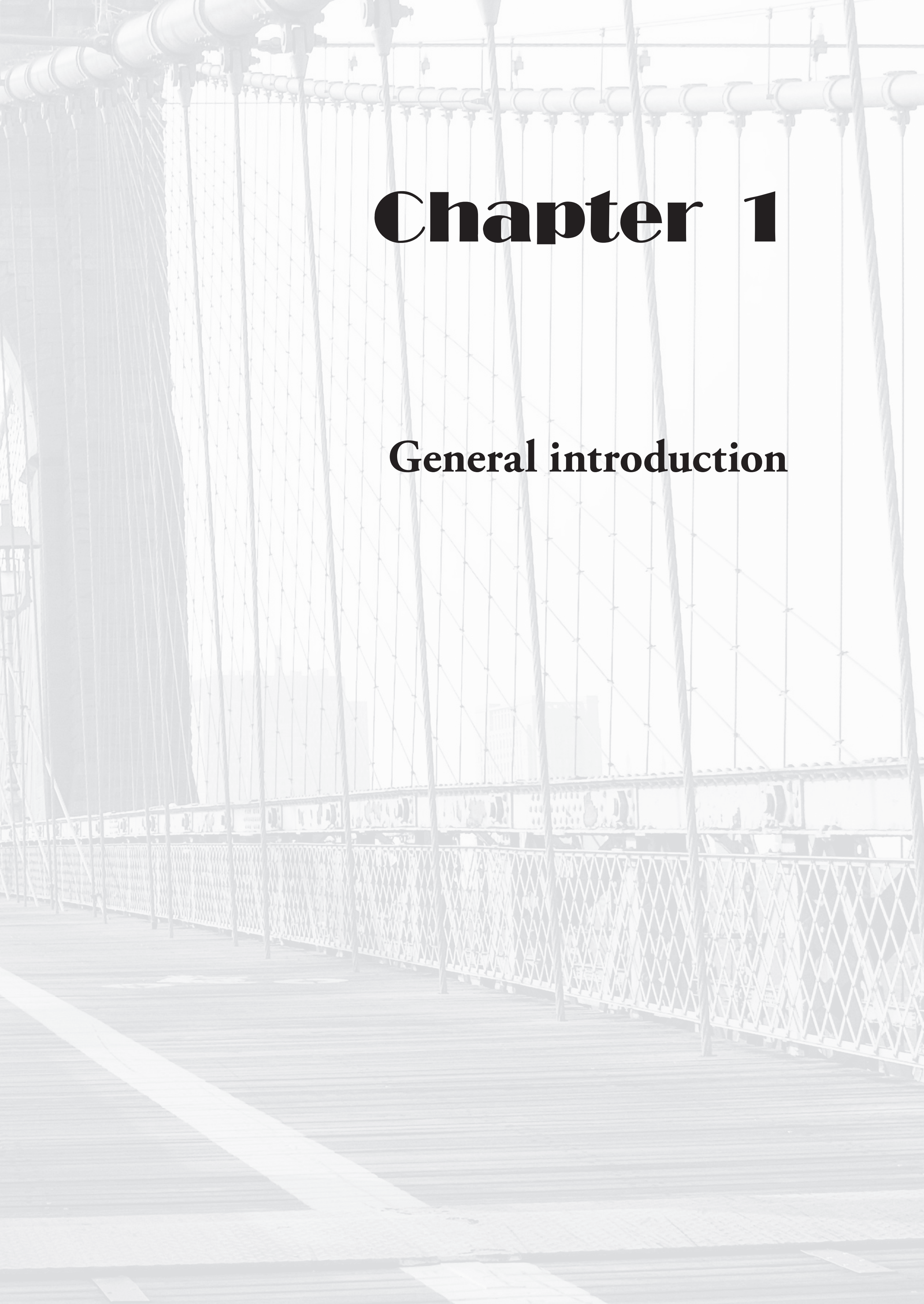
Promotor: Prof. dr. A. Postma

Copromotoren: Dr. S. Van der Stigchel
Dr. T.C.W. Nijboer

TABLE OF CONTENTS

Chapter 1

General introduction



Background

The past years I have encountered many chronic alcoholics with severe declarative memory problems that are associated with the neuropsychiatric syndrome called Korsakoff's syndrome (KS). The majority of them were male, aged 50-60 years, with an unfortunate past of social isolation, unemployment, and often aggression in the course of destructive alcoholism. As Oliver Sacks (1985) described in his case study "The Lost Mariner" in his now famous book "The Man Who Mistook His Wife for a Hat", the declarative amnesia in KS is intense. Oliver Sacks' patient, Jimmie G., was mentally stuck in post-war 1945, although it was in the mid-1970s. Jimmie G. could remember events from the war and the names of aircrafts up to 1945 and constantly celebrated that the war was over. According to the case report, he even spoke with dated words that were in disuse in the 1970s. When he was confronted with recent events and novel developments or his own mirror image, he instantly became frightened as he could not remember anything.

In my initial contact with KS patients their severe memory problems and my personal unfamiliarity with these problems resulted in long discussions on the actual date or the age of the patients. I can remember a participant in my initial research project that kept saying to be 41-years old instead of 59-years old. He became mildly agitated and told me that I should have better manners towards grownups. Another patient could tell me the names of the local football team, but failed to remember that this was the line-up ten years before. Later, when I started to work as a psychologist in Slingedael, an observation and chronic care facility for patients with KS in Rotterdam, I noticed that despite huge general memory problems some patients could relatively easily find their way around in the building. One day, I had lost my cell phone. Lucky for me, one of the patients visited me later in the afternoon and told me: "This must be yours. You better remember were you're keeping your stuff". Some patients that had quite severe disorientation as soon as they entered another room were still able to learn how to walk to a place where they could receive pocket money. Like places, many of the patients were able to remember daily routines. Some of them were even better familiar with the daily routines in the clinic than new members of the care staff. By increasing the number of daily routines it was sometimes possible to give them such a structured day that they required less intensive support and eventually moved to sheltered or independent homes. Their residual capacities could be of use in training capacities needed to live on their own again.

It was intriguing to see residual learning and memory in KS despite the global declarative amnesia. Since learning and memory in KS can support the autonomy of patients with KS, but also provides us insights into the complexity of the human memory system, the primary focus of this thesis is to get a better understanding of residual learning and memory capacities in KS. Moreover, the secondary focus of this thesis is to support accurate diagnosis of the syndrome itself and the social and emotional needs of the patients that are diagnosed with KS.

Wernicke Encephalopathy and Korsakoff's syndrome: the discovery of a multiphase syndrome

Carl Wernicke (1848-1905) was a German Neurologist. He became well-known for the discovery that patients that suffered from brain damage to the left posterior section of the superior temporal gyrus show language impairments. The patients that he described were unable to understand language in its written or spoken form, but could speak with normal grammar, syntax, rate and intonation. This form of aphasia became known as Wernicke's aphasia. Later in his career, in 1881, Carl Wernicke described a quite different illness of the brain characterised by mental confusion, involuntary eye-movements (also called nystagmus) and/or weakness of the eye-muscles (also called opthalmoplegia) and a lack of coordination (also called gait ataxia) (Wernicke, 1881). The syndrome, later known as Wernicke's Encephalopathy (WE), was associated with haemorrhages around the third and fourth ventricle and atrophy of thalamic area in autopsy findings of three patients described by Carl Wernicke (see Figure 1 for comparable findings in recent structural T1 MRI of a patient acutely diagnosed with WE). Two of Carl Wernicke's patients had a history of chronic alcoholism and self-neglect, but the third patient was a young woman who developed persisting vomiting after the incidental ingestion of sulphuric acid. The three patients described by Wernicke died within two weeks of onset of neurological manifestations, suggesting that WE can be fatal (Sechi & Serra, 2007). Six years later, Sergei Korsakoff (1854-1900), a Russian neuropsychiatrist, described memory disturbance in "not less than 30 cases" of chronic alcohol abuse (Korsakoff, 1887; Korsakoff, 1889). All his patients showed a severe impairment of current and recent memory, all asking the same questions over and over again, not being able to recognise people they had just met.

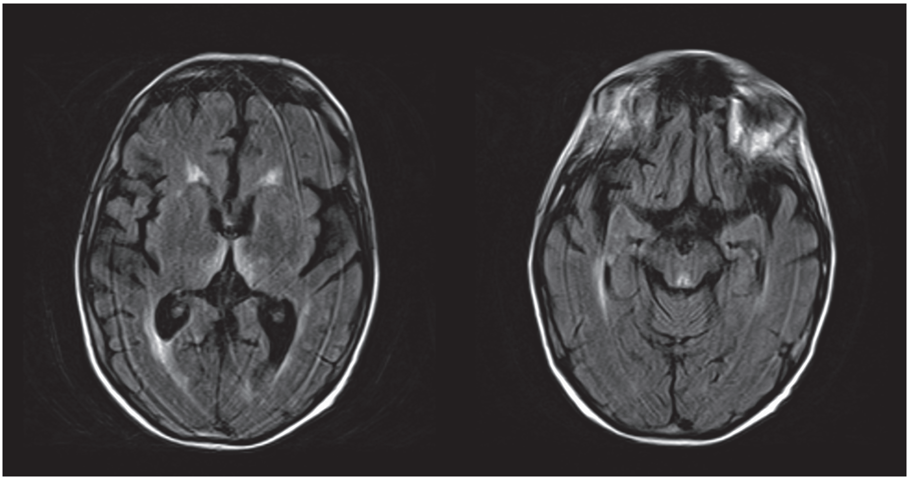


Figure 1. Axial MRI FLAIR showing hyperintense signals (white) in the mesial dorsal thalami (left) and periaqueductal gray matter and tectum (right). Both are common findings in untreated Wernicke's Encephalopathy and are at least in part recoverable by acute parenteral thiamine treatment. Reproduced under Creative Commons Attribution.

Sergei Korsakoff described the salient features of the syndrome that became later known as KS:

1) A severe memory defect, especially for recent events.

2) The falsification of memory (called confabulations) in alert and responsive individuals.

3) Weakness, numbness, pins-and-needles and burning pain (called polyneuropathy) in the hands and feet and sometimes arms and legs.

Importantly, Korsakoff also found the same symptoms in 16 patients that did not have a history of chronic alcoholism, but suffered from other medical conditions such as persistent vomiting (eight cases), infections, poisoning, and post-partum illness, suggesting that not alcohol per se was the causative factor to the syndrome. Although Sergei Korsakoff did not refer directly to the disease described by Carl Wernicke (1881), he did mention that confusion and agitation commonly preceded the memory problems, sometimes accompanied by eye-movement disorders such as nystagmus or opthalmoplegia (Kopelman et al., 2009). Later, it turned out that both Carl Wernicke and Sergei Korsakoff described the same patients, but in different stages of their illness: Wernicke the acute phase and Korsakoff the chronic phase.

In the 1940s, Campbell and Russell hypothesized a nutritional association of WE and suggested thiamine (vitamine B1) deficiency as a causative factor (Sechi & Serra, 2007). Later, the physicians de Wardener and Lennox (1947) confirmed that thiamine was the causative factor to WE in a large group of soldiers that were prisoners-of-war during World War II in Singapore. The conditions for the prisoners and the physicians were very poor and the soldiers became malnourished. After months, some prisoners died after a period of confusion, ophthalmoplegia and eventually coma. The circumstances were hostile: they were not allowed to keep written papers but secretly kept them in a jungle grave, their medical instruments were confiscated multiple times and they had huge shortage of medicine. Nevertheless, De Wardener and Lennox were able to describe the effects of acute thiamine treatment versus no thiamine treatment. Many patients of de Wardener and Lennox died when no treatment was available, but some of them survived and at least partially recovered after thiamine treatment. Later, it became known that chronic alcoholics are specifically vulnerable to thiamine deficiency since their lifestyle is characterized by a poor diet and the absorption of thiamine from food is reduced in severe alcoholics due to impaired functioning of the gastrointestinal tract and liver (Zahr, Kaufman, & Harper, 2011). This damage to the body is not fully reversible after quitting alcohol and therefore forms one of the main causes that patients with KS remain specifically vulnerable to novel episodes of thiamine deficiency (Thomson, 2000).

Diagnosis and treatment of Wernicke's Encephalopathy and Korsakoff's syndrome

Since the discovery of this multiphase syndrome the diagnostic and treatment of WE has been established with more certainty due to a large amount of case and group studies on this topic (Lough, 2012). Importantly, Victor and colleagues (1971) noted that contrary to popular belief that WE is always accompanied by KS, partial recovery from WE is the rule and around 21% of the patients recover completely. In the course of decades it has repeatedly been demonstrated that acute treatment of WE with intravenous or intramuscular (parenteral) thiamine replacement therapy in the initial phase of the disease is a life-saving measure that may also prevent the development of chronic brain damage (Thomson & Marhall, 2006; Isenberg-Grzeda et al., 2012). The extent of recovery cannot (yet) be predicted during the acute stage of the illness, but as symptoms progress recovery is less likely (Sechi & Serra, 2007). Although one could expect that WE is currently easily treatable with relatively minor effort, the syndrome is not easily recognized by physicians and confused with states of drunkenness or alcohol-withdrawal-delirium. Sadly, recent estimates proclaim that around 85% of the cases with WE are missed or mislabelled, resulting in patients not been given appropriate intravenous or intramuscular thiamine treatment (Isenberg-Grzeda et al., 2012). Although this issue has received attention in many scientific journals, the underdiagnosis and undertreatment still leads to life-threatening situations and severe cognitive problems, such as KS. It is alarming to see that modern medicine is capable of the most advanced high-tech clinical operations, but unable to manage these forms of malnourishment effectively. Chapter 2 of this thesis presents a case-study of a patient who was admitted to the Korsakoff clinic after a prolonged time (> 5 days) without thiamine replacement therapy in the acute phase of WE. Both the timing and severity of the syndrome are discussed in this chapter. Unfortunately, in the chronic phase of KS, cognitive problems can not be ameliorated by thiamine therapy anymore and declarative amnesia is irreversible (Smith & Hilman, 1999). It is nevertheless of importance to keep an increased suspicion for thiamine deficiency in KS, since many of the problems that result in the initial deficiency are not fully reversible (Zahr et al., 2012). New infections could lead to new states of WE resulting in cognitive decline when not actively treated with thiamine (Wijnia & Oudman, 2013).

As mentioned earlier, KS is a disproportionate impairment in memory, relative to other features of cognitive functioning, resulting from thiamine deficiency (Sechi & Serra, 2007). Careful clinical examination for KS is only relevant when the acute state of WE is resolved after at least six weeks of sobriety. KS can also develop insidiously, without a clear cut state of WE (Blansjaar & Van Dijk, 1992). For accurate diagnosis of both instances of KS, extensive neuropsychological assessment is vital since this could give a detailed analysis of the cognitive profile (Wester, Westhoff, Kessels, & Egger, 2013). However, many busy clinical settings ask for quick screening instruments to get an impression of cognitive functioning. Chapter 3 of the current thesis evaluates the applicability of two cognitive screening instruments in the detection of KS that have originally been developed to detect Alzheimer's dementia. The most commonly applied cognitive screening instrument in general as well as psychiatric hospitals is the Mini-Mental State Examination (MMSE). Whether this screening instrument is applicable to screen for KS and whether the MMSE is as good as a novel cognitive screening instrument called the Montreal Cognitive Assessment (MoCA) is discussed in Chapter 3 of the thesis.

Once KS has been established, patients are often in need of lifelong ambulant or clinical care. Many patients with KS reside in nursing homes as forms of intensive sheltered living. Institutionalized patients with KS have not been studied extensively and limited literature is available on the long-term care for KS patients. A central issue in all forms of long-term care is the quality of life of the patients. Questionnaires and observational instruments that are intended to assess quality of life give an overview on general well-being. In chapter 4 of this manuscript quality of life is compared between patients with KS and dementia patients with a proxy-based, observational measure of quality of life. A central diagnostic issue of this chapter is whether dementia services are acquainted with the behavioural characteristics of KS or whether those patients require specific forms of care to accomplish their needs.

Spared and impaired memory capacities in patients with Korsakoff's syndrome

Memory problems are a defining characteristic of KS, but recent studies suggest that despite the severity of the memory problems patients with KS are still able to show residual memory potential (see for example Hayes, Fortier, Levine, Milberg, McGlinchey, 2012 for a review). To better understand this apparent controversy it is important to note that memory is not a unitary construct, but can be devided in many subdomains. In the second part of this thesis the memory problems and residual capacity to learn and memorize in KS are the central theme. The memory problems in KS mainly concern a severe impairment of anterograde declarative memory, with reduced imprinting and recall (Butters et al., 1985; Kopelman et al., 2009). Patients with KS fail to learn and remember novel events after the development of KS. Chapter 5 of this manuscript deals with the question whether verbal or spatial declarative learning and memory are more compromised in KS.Verbal declarative memory refers to process of remembering information that is conveyed in written or spoken words while spatial memory refers to remembering the environment or elements from the environment such as locations of objects around us. Moreover, declarative memory and learning follow a number of operations that have been disentangled in the neuropsychological literature, such as working memory, imprenting and recall. A second aim of this chapter is to elucidate whether the memory problems are most pronounced in one of the memory operations, and if the content interacts with those memory operations. In this study, task performance of patients with KS is compared across four commonly applied neuropsychological tests in order to gain a better understanding of the specific form of amnesia that is central in KS.

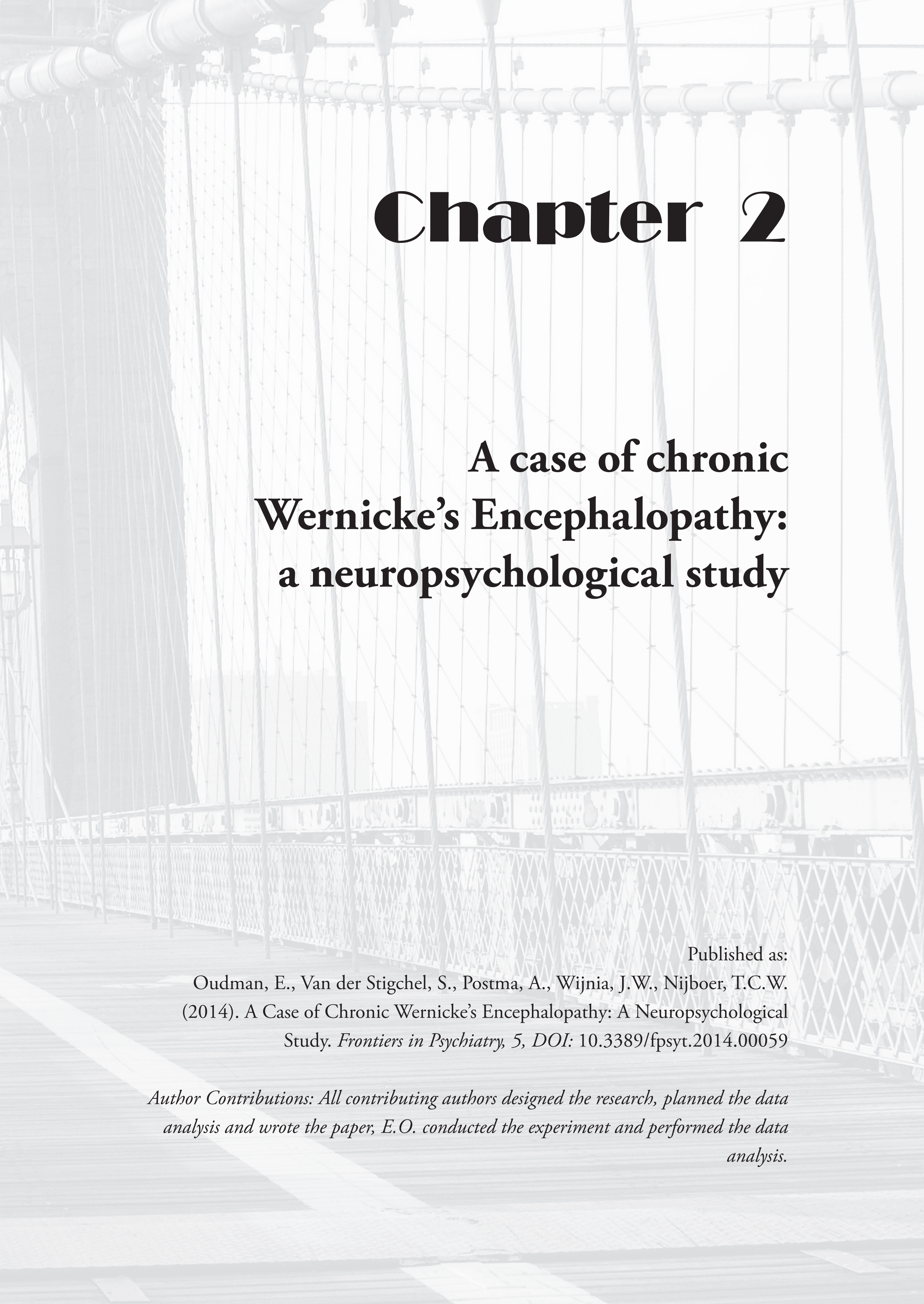
The majority of current research on contextual memory in KS is devoted to explicit memory, while implicit contextual memory has received less attention. A paradigm to investigate implicit spatial learning is the implicit contextual learning task, which was originally developed by Marvin Chun (Chun & Jiang, 1998). Implicit contextual learning is the ability to acquire contextual information from our surroundings without conscious awareness. Such contextual information facilitates the localization of objects in space. In a typical implicit contextual learning paradigm, subjects need to find a target among a number of distractors during visual search. Some of the configurations of stimuli are repeated during the experiment resulting in faster responses than for novel configurations, without subjects being aware of their repetition. In chapter 6 of this thesis the main question is whether patients with KS still have the ability to implicitly learn contextual information in the implicit contextual learning paradigm, despite their marked problems with regard to declarative memory operations. This form of implicit learning is specifically relevant in everyday life, for example if we automatically take the right turn on the road, or if we start searching in the right direction for our keys.

A daily activity which requires processing of implicit as well as explicit information is spatial navigation. Spatial navigation refers to remembering where things are, and applying this information to get from one place to another. It is a complex, dynamic process, involving continuously changing view points, and besides visual cues also a trace of locomotor cues. Our navigation ability depends both on conscious, intentional aspects and more implicit, automatic elements. As an example of the latter, simply following a guide will often allow you to find the way back, as if you unthinkingly had registered the spatial information. In chapter 7 of this thesis the multiple aspects of the memory system that are needed for route learning in KS patients are studied. Here, the primary question is addressed whether KS patients still have residual ability to learn spatial information during spatial navigation, despite their global amnesia. Moreover, the question whether this residual learning is based on automatic rather than effortful processes is explored (Hasher & Zacks, 1979).

Rehabilitation and treatment for patients with Korsakoff's syndrome

Due to the severity of cognitive problems in KS, autonomy is vastly compromised. In the second part of this thesis we explore whether patients with KS still have residual learning potential in various settings despite their global declarative amnesia. In the third part of this thesis the central question is whether any residual learning potential could effectively be applied in the rehabilitation of patients with KS to increase their functional autonomy. While recent studies imply that specific forms of implicit and nondeclarative memory are relatively preserved in KS, it has also been suggested that intact forms of memory in KS are restricted to operate in a rigid automatic fashion (Hayes, et al., 2012). This restriction forms a burden on successful rehabilitation in KS. Moreover, it has been suggested that KS patients may exhibit normal nondeclarative memory performance on a variety of tasks, however when the task requires additional cognitive processes, such as executive functioning, task performance is impaired (Beaunieux, Pitel, Witkowski, Vabret, Viader, & Eustache, 2012). Chapter 8 of this thesis is a review article that has the purpose to increase insights in the available tools for successful memory rehabilitation to support procedural learning and memory in KS. It integrates knowledge from procedural learning ("knowing how") with recent advances from memory rehabilitation and gives suggestions how residual learning can be optimalized in KS.

A specific example of procedural learning that would be relevant for increasing the functional autonomy of patients with KS is presented in chapter 9 of the manuscript. The primary question of this chapter is whether patients with KS are able to learn and maintain a new daily living skill. The memory rehabilitation literature describes two discrepant learning techniques, namely errorless learning and trial and error learning. Trial and error learning is characterised by repeated attempts and errors which are continued until success. In contrast, an essential element of errorless learning is that the patient is not allowed to make errors by eliminating guessing during the process of learning, to support the already comprised memory functioning. Errorless learning is a good candidate for an effective cognitive rehabilitation technique as it is based on residual implicit memory functioning. The main objective of the study presented in this chapter is to examine whether KS patients still have some potential for learning an instrumental activity of daily living and whether errorless learning could be more effective to do so than trial and error learning.



Chapter 2

A case of chronic Wernicke's Encephalopathy: a neuropsychological study

Published as:
Oudman, E., Van der Stigchel, S., Postma, A., Wijnia, J.W., Nijboer, T.C.W. (2014). A Case of Chronic Wernicke's Encephalopathy: A Neuropsychological Study. *Frontiers in Psychiatry, 5, DOI:* 10.3389/fpsyt.2014.00059

Author Contributions: All contributing authors designed the research, planned the data analysis and wrote the paper, E.O. conducted the experiment and performed the data analysis.

Abstract

A 54-year old woman was referred to our Korsakoff Center because of extensive cognitive problems following acute Wernicke's Encephalopathy (WE). She had a relatively short history of alcohol abuse and was found lying on the floor in her home by her son. After five days without treatment she was diagnosed with WE in a general hospital. During the course of the disease minimal change to the acute situation occurred, with chronic confusion, attention deficits and incoherent behavior symptoms most notable unlike classical Korsakoff's Syndrome (KS). Neuropsychological assessment after four and sixteen months after admission to the hospital revealed global cognitive decline, with striking impairments in attentional, executive and memory functions. The present case study suggests that the state of confusion and the neuropsychological symptoms in WE can become chronic in case of very late treatment. We therefore recommend that confused alcoholics should receive appropriate parenteral thiamine according to the current clinical standards.

Introduction

Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome resulting from vitamin B1 (thiamine) deficiency (Manzo, Locatelli, Candrua, Costa, 1994). The syndrome is characterized by confusion, attentional disorders, incoherence, eye-movement disorders and ataxia, although frequently only one or two characteristics are present (Wernicke, 1881; Harper, Giles, Finlay-Jones, 1986, Sechi & Serra, 2007). In the industrialized world, most patients with WE have a background of chronic alcoholism and self-neglect (Kopelman, 2002). WE requires immediate treatment with intravenous or intramuscular thiamine. When patients with WE are promptly treated with parenteral thiamine replacement therapy, this is a life-saving measure that also may prevent the development of chronic brain damage (Thomson & Marshall, 2006). When WE is left untreated or is inappropriately treated with either low doses of thiamine or oral thiamine replacement therapy, this may result in a life-threatening situation with mortality rates up to 20% of the patients (Sechi & Serra, 2007). In the patients that survive this lack of treatment, varying degrees of brain damage develop, although the exact course of illness is not well understood (Isenberg-Grzeda, Haley, Kutner, Nicolson, 2012). Progression into a well-known form of chronic amnesia, Korsakoff's syndrome (KS), is not uncommon (Kopelman et al., 2009, see Figure 1). Usually, KS follows WE when acute confusion improves within one to a couple of weeks. Primary characteristics of this improvement include the ability to concentrate for a longer time, less incoherence in behavior and clear consciousness over the course of the day despite severe amnesia (Kopelman et al., 2009; Jung, Chanraud, Sullivan, 2012; Wijnia & Oudman, 2013). Descriptions of cases of WE were the symptoms do not improve rapidly are scarce and often restricted to the acute situation. Examples of such cases have been described in the course of World War II following starvation in prisoners of war (de Wardener & Lennox, 1947). Descriptions of the cognitive sequalae in the course of prolonged confusion following WE are currently not available in the literature. Such neuropsychiatric descriptions of severe cases of WE are crucial, however, as it will give insight in the severity of the syndrome. Despite the current standards of emergency care in the industrialized world a vast majority of patients with WE are inadequately managed, resulting in patients that show confusion for a prolonged time (Thomson, Marshall, Bell, 2013; Isenberg–Grzeda, Chabon & Nicolson, 2014; Oudman & Wijnia, 2014). Here, we present a case study that illustrates the cognitive and behavioral characteristics, including signs of confusion, of a patient who was admitted to our clinic with untreated WE. Neuropsychological assessment revealed striking cognitive impairments unlike Korsakoff's syndrome. Importantly, the initial cognitive and neuropsychiatric problems did not resolve in time, providing an example of a patient with acute WE that became chronic.

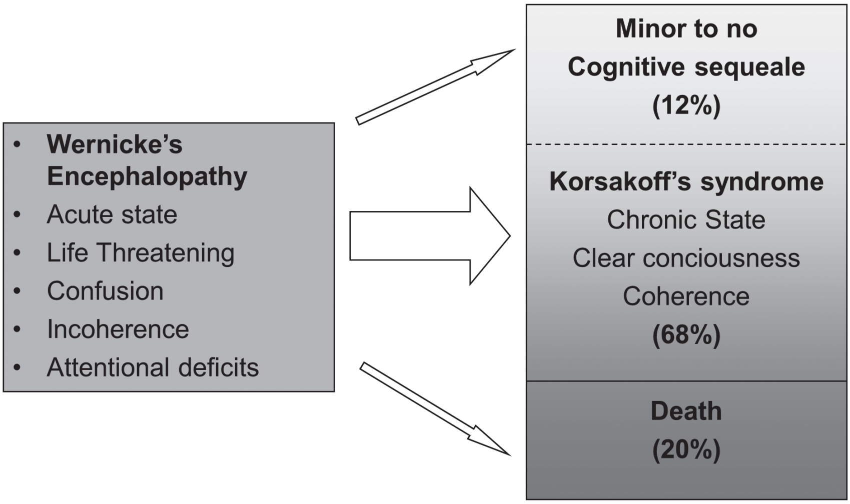


Figure 1. Evolution of Wernicke's Encephalopathy as proposed by Harper et al., 1986 and Day et al., 2008. See Kopelman et al., 2009 for a review.

Case report

Biographical history

According to members of the family, the patient functioned independently prior to the neurological problems. The son of the patient visited her several times a week. In her house she was able to manage the household, despite her alcohol abuse. The amount of alcohol she consumed varied between one and three bottles of wine each day. She divorced twelve months prior to diagnosis with WE. Up until six months before admission the patient worked in a reel kitchen in a hospital. The last month, she had not been eating well and consumed alcohol throughout the day. He told that the patient did not feel like eating, but still spoke about things she wanted to undertake to manage her alcoholism. The day before she was found, she had a telephone call with her son. The son reported that the telephone call included a regular exchange of information without any striking exchange of information.

Medical history

Our patient is a 54-year old woman with a 7-year history of alcohol abuse. The patient did not have a psychiatric history. She was found in her house on the floor of the living room. According to reports of her son who found her, she was unable to move her legs, showed odd eye movements, had visual hallucinations of food lying around her, talked nonsense and was incontinent of urine. After a visit of a general practitioner to her house, her son was told to give his mother rest. After five days and no apparent change to her situation, a visiting psychiatrist referred her to the hospital where she was diagnosed with WE and underwent a therapy of oral thiamine treatment. Subsequently, the patient was admitted to a department of an addiction center where she stayed for almost eight months. Here her behavior was described as incoherent and confused. She showed a compulsion to visit the toilet regularly and to frequently ask the nursing staff for cigarettes. After her stay in the addiction center she was referred to our clinic for patients with KS.

Methods

Four months after she was found a neuropsychological evaluation was performed (T1) in the addiction center. Sixteen months after the first evaluation, the cognitive functions were re-evaluated (T2). Results of the first and second neuropsychological evaluation are displayed in Table 1. A chronic KS reference group is displayed in the last column. The results for the reference group were adopted from group studies on chronic KS patients as displayed in Table 1. The first neuropsychological evaluation consisted of the Wechsler Adult Intelligence Scale - III (Uterwijk, 2000), the Raven Standard Progressive Matrices (Raven, Raven, Court, 1995), Word Fluency Animals and Professions (Mulder, Dekker, Dekker, 2006), Digit Span Forward and Backward (Uterwijk, 2000), Rey's Complex Figure Task (Meyers, & Meyers, 1995), Wechsler Memory Scale -R, Hooper Visual Integration (Walker, 1956), Stroop (Hammes, 1971), Trail Making Task (Tombaugh, 2004), and the Behavioural Assessment of Dysexecutive Syndrome Key Search Task. The second neuropsychological assessment consisted of the Mini-Mental State Examination, the Cognitive Screening Task (de Graaf & Deelman, 1991), Word Fluency Animals, Digit Span Forward and Backward, Trail Making Task, the Visual Association Test (Lindeboom, Schmand, Tulner, Walstra, Jonker, 2002), Rey's Complex Figure Task and the Frontotemporal Dementia Rating Scale (Mioshi, Hsieh, Savage, Hornberger, Hodges, 2000). The patient was informed by the first author and asked whether she was willing to participate. Written informed consent was obtained from the legal representative. The procedure was performed in accordance with the guidelines of the Declaration of Helsinki and guidelines for recruitment of incompetent patients (cf. Meulenbroek et al., 2010).

Results

Observations and neuropsychological assessment on T1

Qualitative observations on T1 showed a consistent pattern of striking impairments. Mental confusion was reported, with a preference to keep asking for cigarettes, high distractibility and disorganization of behavior. The patient would frequently walk away during a conversation. Her behavior appeared severely disorganized. While she was sitting behind a computer performing Solitaire, she would move her legs up and down vigorously, possibly as a symptom of late-stage WE (Sechi & Serra, 2007). Moreover, she would walk into her room, undress, lay in her bed for just a couple of minutes. Hereafter she would dress herself, ask the nursing staff for cigarettes, smoke and walk into her room to undress and lay in her bed for just a couple of minutes and dress again. During lunch and dinner time she walked into the room and would just eat one bite and leave the room instantly. During the nights, she would ask the staff for food. According to nursing staff reports, she did not show evidence of positive nor negative emotions during the day.

The left column of Table 1 depicts the test scores on neuropsychological assessment after four months after admission to the hospital. Initially (T1), her performance on the neuropsychological assessment was consistent with a profile of cognitive deterioration, showing impaired performance on tests for attention, orientation, intelligence, word fluency, working memory, long-term memory, construction and executive functioning, compared to healthy participants. Importantly, the cognitive profile was severely affected by the attentional disorders, consistent with an acute WE. Neuropsychological performance ranged from moderate to severe impairment, with the exception of perceptual abilities. The reference groups of KS patients had an impaired performance on orientation, long-term memory and executive functioning. On tasks intended to index orientation, word fluency, working memory, visuoconstruction, and intelligence the performance of the patient was more than one standard deviation below the average score in the KS reference groups. This suggests that both the nature and extent of cognitive disorders in the case study were remarkably serious.

Table 1. Test results of neuropsychological assessment after four months and sixteen months after admission to the hospital in our case and a KS reference group.

	Case: Neuropsychological Assessment 1 - four months after admission			**Case: Neuropsychological Assessment 2 - sixteen months after admission**			
Cognitive Domain	Test	Patient	Patient compared to KS reference group	Test	Patient	Patient compared to KS reference group	KS reference group
Orientation	Time and Place (MOCA)	2**	*z* = -1.1	Time and Place (MOCA)	2**	*z* = -1.1	3.6 (1.5)[1]
Global Cognitive Functioning				MMSE¶	21/30**	*z* = -0.6	22.8 (3)[2]
				Cognitive Screening Test¶	10/20**		N.A.
Language	Word Fluency Animals (1 min) ¶	15**	*z* = -1.1	Word Fluency Animals (1 min) ¶	10**	*z* = -1.3	36 (20) [3]
	Word Fluency Professions (1 min) ¶	13**	*z* = -1.5				35 (15) [3]
Working Memory	Digit span ¶	5*	*z* = -3.9	Digit span¶	8*	*z* = 0.4	7.7 (0.7) [2]
Long-Term Memory	Rey's complex figure recall¶	0**	*z* = -0.9	Rey's complex figure recall§	0**	*z* = -0.9	2.5 (2.7) [4]
	WMS-R Logic Memory ¶	7**					6 (-)[5]
	WMS-R Visual Reproduction ¶	0**			0**		
				Visual Association Test§			N.A.
Visuoperception	Hooper Visual Integration	15					N.A.
Visuoconstruction	Rey's complex figure (copy) §	13*	*z* = -2.9	Rey's complex figure (copy)	11*	*z* = -3.2	29.8 (5.8) [2]
Attention	Stroop I §	3**	*z* = -0.5				12.9 (18.3) [3]
	Stroop Interference score (III to II) §	42	*z* = 0.8	TMT A§	4**	*z* = -0.6	26.5 (18.9) [3]
	TMT A §	7*	*z* = -0.5				24.8 (32.5) [3]
	TMT Interference score (B to A) §	24*	*z* = -0.3				32.2 (29.5) [3]
Executive Functioning	BADS Key Search¥	1**	*z* = -0.8				2.0 (1.2) [3]
				FDS- Rating Scale¶	5/30**		N.A.
Intelligence	WAIS-III	70**	*z* = -2.4				104 (14) [5]
	WAIS-III verbal scale	74**	*z* = -2.4				107 (14) [5]
	WAIS-III performal scale	65**	*z* = -2.3				100 (15) [5]

N.A. = Not Available, * Below average performance compared to the healthy control norm group (≤16th percentile). ** Impaired performance compared to the healthy control norm group (≤6th percentile).¶ Raw score § Percentile score ¥ Equivalent score (max 4)

[1]. A reference group of 20 patients with KS, with an average age of 57.6 (8.7) years (Wester, Westhoff, Kessels, Egger, 2013).
[2]. A reference group of 16 patients with KS, with an average age of 58.9 (7.1) years (Oudman, Nijboer, Postma, Wijnia, Kerklaan, Lindsen, Van der Stigchel, 2013).
[3]. A reference group of 19 patients with KS, with an average age of 58.8 (8.8) years (Kessels, Kortrijk, Wester, Nys, 2008).
[4]. A reference group of 20 patients with KS, with an average age of 59.7 (5.7) years (Fujiwara et al., 2008).
[5]. A reference group of 30 patients with KS, with an average age of 60.5 (10.0) years (Welch, Cunningham, Eckardt, Martin, 1997).

Observations and neuropsychological assessment on T2

Qualitative observations of confused behavior lasted during her stay in our Korsakoff clinic without showing any signs of improvement or deterioration over time. The patient appeared as highly distractible if the team members were able to motivate her. She would frequently undress and redress herself in her room.

The right column of Table 1 depicts the test scores on neuropsychological assessment after sixteen months after admission to the hospital. The pattern of cognitive functioning was consistent to the pattern of observed cognitive dysfunction at T1. The patient showed similar performance on the cognitive tasks: impaired performance on tests for orientation, intelligence, word fluency, working memory, long-term memory, construction, attention and executive functioning compared to healthy participants. Attentional problems were as striking as at T1. The cognitive pattern was stable compared to T1, whereas improvement in case of KS is to be expected based on the available literature (see Figure 1).

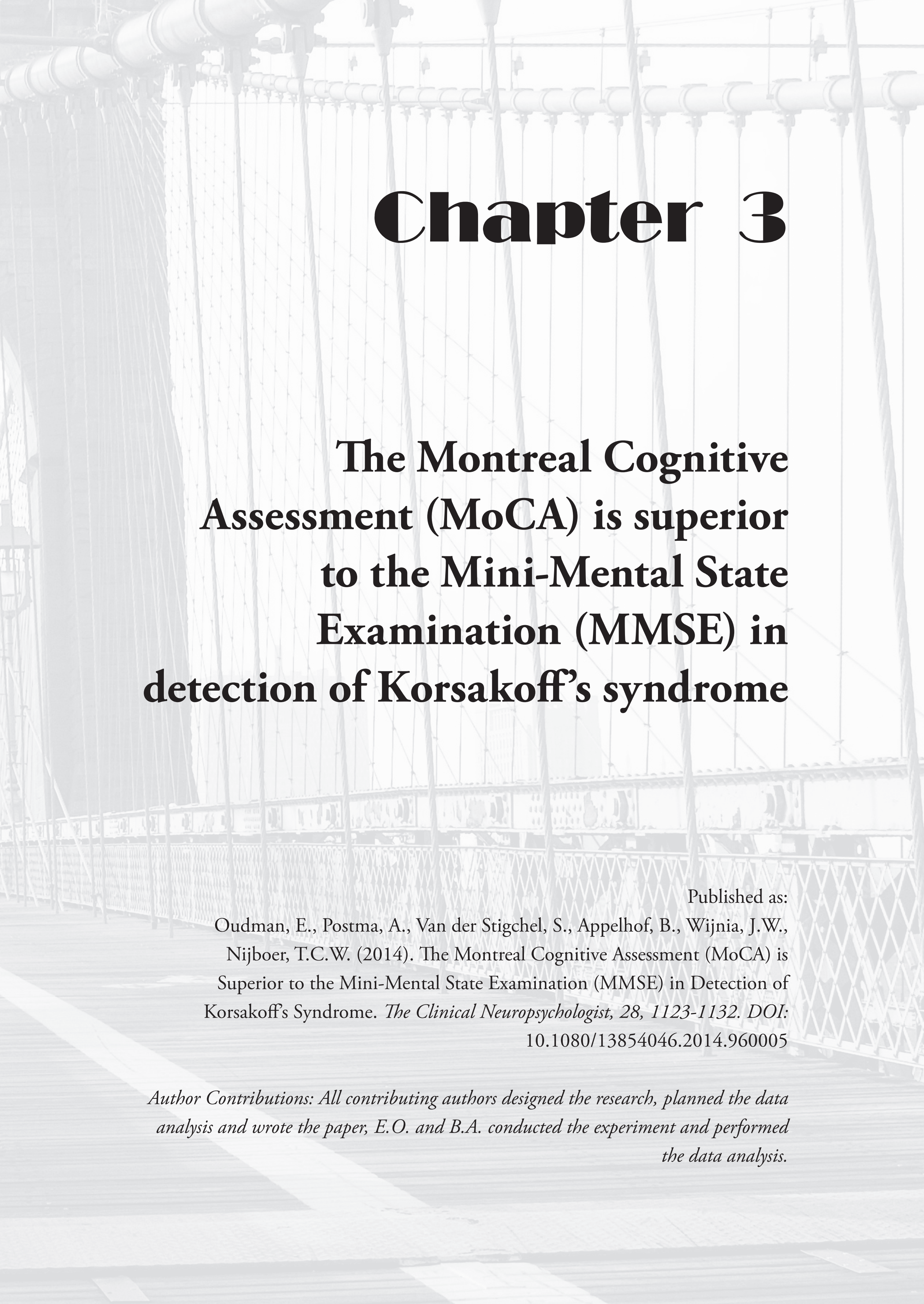
Discussion

The patient in the present case report showed a distinctive chronic pattern of cognitive and neuropsychiatric impairments in the course of severe WE. Signs of confusion and incoherent behavior were evident and did not resolve in time. Cognitive disorders in attention, long term memory, working memory, visuoconstruction, word-fluency became apparent both after four and sixteen months after admission to the hospital. Importantly, the attentional deficits severely affected the cognitive profile on both neuropsychological evaluations. Compared to a KS reference group, the patient showed a broader range of severe cognitive impairments. The patient was able to function independently up to the point that she developed WE. The cognitive and neuropsychiatric problems were in accordance to the acute symptoms of WE and did not improve over the course of her stay in the clinic, suggesting that her WE became chronic.

WE is a life-threatening condition following acute thiamine deficiency (Kopelman, 2002). Whereas a large deal of research on WE has been devoted to successful treatment of WE in the acute phase, descriptions of cases were confusion does not improve rapidly are currently lacking. This is striking given that in clinical practice, WE is undertreated and patients are still admitted to general or psychiatric hospitals with prolonged states of confusion (Thomson et al., 2013; Isenberg–Grzeda et al., 2014; Oudman & Wijnia, 2014). Moreover, WE is potentially fatal in about 20% of the patients (Kopelman et al., 2009). The present case study suggests that WE can not only result in a life-threatening acute situation, but also in a chronic form of WE, incorporating a chronic state of confusion and disorganized behavior. The severity of the neuropsychiatric symptoms make a patient in need of lifelong care. A possible explanation for why the patient in the current case study developed a severe chronic pattern of cognitive problems could be the late hospital admission and inadequate treatment with thiamine replacement therapy. Although the patient was found lying on the floor with abundant symptoms of neurological disease (e.g. odd eye movements, visual hallucinations, incontinence), she was not admitted to the hospital in the first five days and received no treatment during this period. Since severe cognitive disorders are the consequence of untreated or under-treated thiamine deficiency, the patient should have received thiamine replacement therapy instantly (Isenberg-Grzeda et al., 2012).

In the present case, WE was eventually diagnosed in the hospital, after which oral thiamine suppletion started. This time point of thiamine suppletion is regarded as a very late compensation for thiamine deficiency (Thomson et al., 2013). Moreover, oral replacement therapy is less effective than parenteral replacement therapy (Sechi & Serra, 2007). Given that the prognosis of WE is known to depend on the speed of compensating the deficiency in thiamine (Isenberg-Grzeda et al., 2014) and the severe chronic cognitive disturbance associated with chronic WE observed in the present study, our results indicate that an active treatment policy is needed to avoid severe chronic neuropsychiatric symptoms. Current treatment standards suggest that parenteral (intravenous or intramuscular thiamine should be given 200mg up to 500mg three times daily until symptoms of acute WE resolute (Thomson et al., 2002). In order to prevent severe and chronic cognitive disorders, physicians should have a high index of suspicion for WE and dose parenteral thiamine accordingly (Isenberg-Grzeda et al, 2012).

Although the patient in our case study had a history of alcohol abuse, the neurocognitive symptoms had an acute onset as reported in WE, which makes alcohol dementia an implausible explanation for the severe acute cognitive problems (Oslin, Atkinson, Smith, Hendrie, 1998). Moreover, the cognitive problems remained stable over a period of sixteen months, unlike progressive dementia. Dissimilar to KS, the patient had chronic problems in her attentional function, working memory, visuoconstruction and word-fluency functions. In conclusion, the current case study illustrates the cognitive and behavioral characteristics of a patient who was admitted to our clinic with untreated WE. Our description provides the first report on a patient with prolonged states of confusion following WE, suggesting that WE can become chronic in case of late thiamine replacement therapy.



Chapter 3

The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) in detection of Korsakoff's syndrome

Published as:
Oudman, E., Postma, A., Van der Stigchel, S., Appelhof, B., Wijnia, J.W., Nijboer, T.C.W. (2014). The Montreal Cognitive Assessment (MoCA) is Superior to the Mini-Mental State Examination (MMSE) in Detection of Korsakoff's Syndrome. *The Clinical Neuropsychologist, 28, 1123-1132. DOI:* 10.1080/13854046.2014.960005

Author Contributions: All contributing authors designed the research, planned the data analysis and wrote the paper, E.O. and B.A. conducted the experiment and performed the data analysis.

Abstract

The Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) are brief screening instruments for cognitive disorders. Although these instruments have frequently been used in the detection of dementia, there is currently little knowledge on the validity to detect Korsakoff's syndrome (KS) with both screening instruments. KS is a chronic neuropsychiatric disorder associated with profound declarative amnesia after thiamine deficiency. A representative sample of 30 patients with KS and 30 age-, education-, gender- and premorbid-IQ-matched controls was administered the MoCA and MMSE. The area under the receiver operating characteristic curve (AUC) was calculated in addition to the sensitivity, specificity, positive predictive value and negative predictive value for various cut-off points on the MoCA and MMSE. Compared with the MMSE, the MoCA demonstrated consistently superior psychometric properties and discriminant validity [AUC: MoCA (1.00 SE:.003)] and MMSE (0.92 SE:.033)]. When applying a cut-off value as suggested in the manuals of both instruments, the MMSE (<24) misdiagnosed 46.7% of the patients, while the MoCA (<26) diagnosed all patients correctly. As a screening instrument with the most optimal cut-offs, the MoCA [optimal cutoff point 22/23, 98.3% correctly diagnosed] was superior to the MMSE [optimal cutoff point 26/27, 83.3% correctly diagnosed]. We conclude that both tests have adequate psychometric properties as a screening instrument for the detection of KS, but the MoCA is superior to the MMSE for this specific patient population.

Introduction

Cognitive assessments are clinical examinations to correctly diagnose individuals with cognitive disorders. However, comprehensive cognitive testing is time-consuming, requires skilled clinicians and is demanding for the patient. Therefore, brief screening tools are often applied to obtain an impression regarding cognitive performance of the patient.

The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1974) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005) are two commonly used brief screening instruments for cognitive impairment. The MMSE was originally developed to screen for dementia in a psychiatric setting, and has been shown to have a good sensitivity and specificity as such (Folstein et al., 1974; Cullen, O'Neill, Evans, Coen, & Lawlor, 2007). The MoCA is another brief screening instrument for dementia and Mild Cognitive Impairment (MCI) and is thought to assess a broader array of cognitive domains than the MMSE (Nasreddine et al., 2005). Currently there is debate on the validity of the MMSE as a screening instrument to assess cognitive impairment in certain patient populations. A recent meta-analysis showed that the MMSE has limited value in making a diagnosis of MCI against healthy controls (Mitchell, 2009). Moreover, the MMSE lacks items that index executive functioning and is therefore less sensitive in the detection of patients with specific executive deficits (Mickes et al., 2009). Nevertheless, the MMSE is currently the most commonly used screening instrument for cognitive disorders (Gluhm et al., 2013). Although the MoCA has been less extensively studied than the MMSE, recent studies show that the MoCA could be successfully applied as a screening for MCI (Nasreddine et al., 2005; Hoops et al., 2009) and the instrument successfully detects executive dysfunction in Alzheimer's disease, Parkinson's disease and Huntington's disease (Nasreddine et al., 2005; Hoops et al., 2009; Gluhm et al., 2013). Recently, the MoCA was also identified as a useful screener with good discriminatory power in Korsakoff's syndrome (KS) (Wester, Westhof, Kessels, & Egger, 2013).

KS is a chronic neuropsychiatric disorder associated with profound declarative amnesia. Often the syndrome is the result of thiamine deficiency after prolonged alcoholism (Kopelman, 2002). Commonly executive cognitive dysfunction is also present (Van Oort & Kessels, 2009; Maharasingam, Macniven, & Mason, 2013). Although widely used in various neurological and psychiatric patients in a variety of settings, there are currently no studies available on the usability of the MMSE in KS. Moreover, no study has yet compared the psychometric properties and validity of the MMSE and MoCA in KS. This is remarkable in light of the fact that Korsakoff's syndrome is common in alcoholics. Recent studies suggest that up to 15% of the alcoholics have KS (see Zahr, Kaufman, Harper, 2012 for a review). Cognitive screening could dramatically improve the recognition of KS in alcoholics. There is growing evidence that cognitive impairment contributes to poor treatment outcome in treatment of alcoholism, stressing the importance of versatile cognitive screening in all alcoholics (Alterman, Kusher, & Holohan, 1990). Given these considerations, the aim of the present study was to examine the usefulness of the two screening instruments, i.e. the MoCA and the MMSE, in a group of KS patients. We compared the psychometric properties and diagnostic validity of the screening instruments for this patient group.

Methods

Participants and procedure

The MoCA and MMSE were administered by the same psychologist on the same day in randomly assigned counterbalanced order in 30 patients diagnosed with KS and 30 age-, education-, gender- and premorbid IQ-matched controls. Between administration of the MoCA and the MMSE there was a 5 minute pause between administration of both tasks. The controls were volunteers who came to our attention through advertising online or by word of mouth. The patients were inpatients of the Korsakoff Center, 'Slingedael', Rotterdam, the Netherlands. All patients fulfilled the DSM-IV criteria for alcohol-induced persisting amnestic disorder (APA, 2000) and the criteria for KS described by Kopelman (2002). All patients were in the chronic, amnestic stage of the syndrome; none of the patients had confusional Wernicke psychosis at the time of testing. All patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts or family reports. All patients were abstinent from alcohol for at least six months. General exclusion criteria were presence of neurological disorders (moderate to severe traumatic brain injury, stroke, epilepsy or brain tumor), illiteracy, and acute psychiatric conditions (psychosis, major depression, etc.), or physical conditions interfering with the testing procedure. Exclusion criteria were verified through inspection of medical charts or family reports. For both the patients and the control group, education level was assessed using seven categories, 1 being the lowest (less than primary school) and 7 being the highest (academic degree) (Verhage, 1964). Premorbid IQ was estimated for both patients and controls with the Dutch Adult Reading Test (Schmand, Lindeboom, & van Harskamp, 1992). The project was conducted according to the declaration of Helsinki and informed consent was obtained.

MMSE

The MMSE consists of 30 items intended to index orientation, registration, attention and calculation, recall and language. The maximum possible score is 30 points, with a score <24 considered as an indication for cognitive decline or dementia (Folstein et al., 1974).

MoCA

The MoCA (Dutch version 1) consists of 13 tasks organized into seven cognitive domains including executive functioning, naming, memory, attention, naming, abstraction and orientation. A total score was generated by summing scores across the seven domains. One point was added for persons with the Dutch educational level 4 or lower (Verhage, 1964; Nasreddine et al., 2005; Wester et al., 2013). The maximum possible score is 30 points, with a score <26 considered as an indication for cognitive impairment.

Statistical analysis

Receiver operating characteristics (ROC) were used to calculate the Area Under the Curve (AUC) for the MMSE and MoCA with SigmaPlot (Systat Software, San Jose, CA). The AUC varies between 0.5 and 1. The ideal test has an AUC of 1, meaning 100% sensitivity and specificity. The sensitivity and the specificity for various cut-off points of the MMSE and MoCA were determined (sensitivity = true positives/true positives + false negatives; specificity = true negatives/true negatives + false positives). When evaluating the usefulness of a screening measure to identify individuals with cognitive disorders, a good sensitivity (>80%) is required, while maintaining a low false positive rate (specificity > 60%) (Blake, McKinney, Treece, Lee, & Lincoln, 2002). Moreover, positive predictive values (PPV), negative predictive values (NPV) and percentage correctly diagnosed in the current sample were calculated. Pearson's correlation coefficients were calculated between the MoCA and MMSE score and (1) age and (2)an index of premorbid IQ. Spearman's rank correlation coefficient was calculated between the MoCA and MMSE score and level of education (Verhage, 1964).

Results

Clinical characteristics and demographic variables

Table 1 shows a summary of clinical characteristics and demographic variables of the patients and controls. No statistically significant differences between the patients and controls were found on clinical characteristics or demographic variables.

Table 1. Summary of demographic variables for all participants

Measurement	Patients	Controls	Significance
Number (number of males)	**30 (24)**	**30 (24)**	
Age	**59.5 (8.9)**	**60.3 (7.2)**	**t(58) = .34**
Educational level mode (range)[a]	**5 (2-7)**	**4 (3-7)**	**U(58) = 1.64**
IQ estimation μ (SD)[b]	**99.2 (8.3)**	**103.6 (10.7)**	**t(58) = 1.76**
MMSE (SD)	**23.2 (3.3)**	**28.2 (1.8)**	**t(58) = 7.23******
MoCA (SD)	**18.1 (3.9)**	**27.1 (1.9)**	**t(58) = 11.18******

Note. * * = statistically significant (p<.05). *** = statistically significant (p<.01). **** = statistically significant (p<.001). MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; a Educational level was assessed in 7 categories: 1: less than primary school (1-5 years of education); 2: primary school (6 years of education); 3: prolonged primary school (7-8 years of education); 4: lower secondary school (7-9 years of education); 5: secondary school (7-11 years); 6: higher secondary school and/or university bachelor degree (7-16 years of education); 7: university master degree or Phd (17-20 years of education (Verhage, 1964). b IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

MoCA versus MMSE

When applying a cut-off value of 24 for the MMSE, which is a frequently used cut-off for hospitalized patients, 14 patients (46.7%) were misclassified as cognitively intact by the MMSE. No patients were incorrectly classified when a cut-off of 26 for the MoCA was used. When differentiating patients with KS from controls, the MMSE had an ROC AUC of 0.92 [95% CI .85 - .98, SE =.033] and the MoCA had an ROC AUC of 1 [95% CI 0 -1 SE=.003], indicating that the MoCA can perfectly discriminate patients with KS from controls with a confidence interval of 95%. Also, the MMSE has rather good discriminative abilities. The ROC-curve is presented in Figure 1 and the sensitivity and specificity is presented in Table 2.

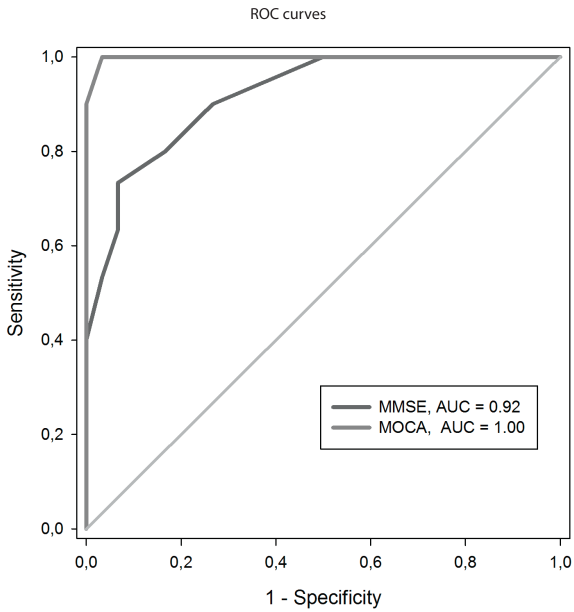


Figure 1 - Receiver Operating Characteristics (ROC) curve for the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) in 30 patients diagnosed with Korsakoff's syndrome and 30 age-, education-, gender- and premorbid IQ-matched controls.

The optimal screening cut-offs are 26/27 (81.7-83.3% correctly diagnosed) for the MMSE and 22/23 for the MoCA (95-98.3% correctly diagnosed) (see Table 2). The optimal proportion of correctly diagnosed individuals was significantly higher for the MoCA compared to the MMSE ($z = 2.8$, $p<.01$). As could be inspected in Table 2, the screening cut-off of 23 for the MoCA has nearly perfect PPV, NPV and Likelihood Ratios.

Correlational analysis

To investigate possible relations between both screening instruments and the clinical characteristics we computed several correlations. Correlation coefficients should be interpreted with caution, since the number of participants was rather small. Results are displayed in Table 3. The MMSE and MoCA showed a very strong positive relationship in patients and a strong positive relationship in controls. This suggest that despite psychometric differences between both screening instruments , there is also a strong consistency in performance on the tasks. Moreover, in controls, but

Table 2. Discriminant validity for the the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for diagnosis of Korsakoff's syndrome.

MMSE Cutoff	Sensitivity (%)	Specificity (%)	Correctly diagnosed (%)	PPV (%)	Positive Likelihood Ratio	NPV (%)	Negative Likelihood Ratio	MoCA Cutoff	Sensitivity (%)	Specificity (%)	Correctly diagnosed (%)	PPV (%)	Positive Likelihood Ratio	NPV (%)	Negative Likelihood Ratio
								<7.5	6.7	100	51.7%	100	Infinite	50.8%	0.9
								<11	10	100	53.3%	100	Infinite	51.7%	0.9
								<14	26.7	100	55%	100	Infinite	52.6%	0.7
<16	6.7	100	51.7%	100%	Infinite	50.8%	0.9								
								<16.5	30	100	63.3%	100	Infinite	57.7%	0.7
								<17.5	50	100	65%	100	Infinite	58.8%	0.5
<18.5	10.0	100	53.3%	100%	Infinite	51.7%	0.9	<18.5	67.7	100	75%	100	Infinite	66.7%	0.3
<19.5	20.0	100	55%	100%	Infinite	52.6%	0.8	<19.5	76.7	100	83.3%	100	Infinite	75%	0.2
<20.5	33.3	100	60%	100%	Infinite	55.5%	0.7	<20.5	86.7	100	88.3%	100	Infinite	81.1%	0.1
								<21	90	100	88.3%	100	Infinite	81.1%	0.1
<21.5	40	100	66.7%	100%	Infinite	60.0%	0.6								
<22.5	53.3	100	70%	100%	Infinite	62.5%	0.5	<22.5	100	100	95%	100	Infinite	90.9%	0
<23.5	63.3	96.7	76.7%	94.1%	19.2	67.4%	0.4	<23.5	100	96.7	98.3%	96.8	30.3	100%	0
<24.5	73.3	93.3	78.3%	90.4%	10.9	71.8%	0.3	<24.5	100	86.7	93.3%	88.2	7.5	100%	0
<25.5	80	93.3	83.3%	91.7%	11.5	77.8%	0.2	<25.5	100	80	90%	83.3	5.0	100%	0
<26.5	90	83.3	81.7%	82.8%	5.4	80.6%	0.1	<26.5	100	63.3	81.7%	73.2	2.7	100%	0
<27.5	100	73.3	85%	77.1%	3.8	88%	0	<27.5	100	40	70%	62.5	1.7	100%	0
<28.5	100	50	75%	66.7%	2.0	100%	0	<28.5	100	30	65%	58.8%	1.4	100%	0
<29.5	100	26.7	63.3%	57.7%	1.4	100%	0	<29.5	100	10	55%	52.6%	1.1	100%	0

Note. Grey areas indicate acceptable sensitivity (>80%) and specificity (>60%) (Blake et al., 2002). Borders indicate the best possible cut-off. PPV = Positive Predictive Value; NPV = Negative Predictive Value; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment.

not in patients, the MMSE showed a strong positive relationship with a task intended to index premorbid intellectual functioning. In KS patients the performance on the MMSE thus could be independent of intellectual functioning. While the MoCA score showed a moderate positive relationship with the level of education in controls, the relation was not significant in patients. This demonstrates that within-group performance variations in KS patients on the MoCA are not related to academic skills.

Table 3. Pearson's correlations (MoCA, MMSE, Age, Premorbid IQ) and Spearman's correlation (Level of Education) between the demographic variables and test performance in 30 patients diagnosed with Korsakoff's syndrome (in grey) and 30 age-, education-, gender- and premorbid-IQ matched controls (in white).

	MoCA	MMSE	AGE	Premorbid IQ	Level of Education
MoCA		.73****	-.11	.19	-.10
MMSE	.60***		-.06	.13	.10
AGE	-.36	-.20		.05	-.10
Premorbid IQ	.28	.53***	-.08		.26
Level of Education	.40**	.34	-.08	.43**	

Note. * * = statistically significant (p<.05). *** = statistically significant (p<.01). **** = statistically significant (p<.001). MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; Premorbid IQ = Estimated premorbid intelligence with the Dutch Adult Reading Test (Schmand et al., 1992).

Discussion

In the current study, we analyzed performance on two screening instruments, the MoCA and the MMSE, in a representative sample of KS patients and age-, education-, gender- and premorbid-IQ matched controls to evaluate their psychometric properties and discriminant validity for assessing cognitive impairment. The results suggest that the MoCA is superior to the MMSE in detecting cognitive disorders in KS. The MoCA displayed excellent diagnostic accuracy in discriminating patients with KS from cognitively intact controls. Both the discriminant validity (optimal sensitivity and specificity, PPV, NPV and Likelihood Ratios) and the percentage correctly diagnosed patients were higher for the MoCA than the MMSE. The optimal cutoff point for detecting KS that allowed a maximization of the sensitivity and specificity was below 22/23 points, with a near to maximum PPV and NPV for a cut-off of 23 points. All indices for discriminant validity were consistent and higher than the respective MMSE values, suggesting that the MoCA has accurate psychometric properties and diagnostic validity to detect KS with a cut-off of 23 points. This cutoff is equivalent to the optimal cutoff point established in a previous validation study for the MoCA for KS (Wester et al., 2013).

Although the MMSE is widely used in a variety of settings, this is the first study to investigate the usability of the MMSE in KS. In the current sample, the optimal cutoff of the MMSE to detect KS was 26/27 points. Specificity and sensitivity were both acceptable for this cut-off (see Table 2), whereas the traditional cut-off of 23 points resulted in 46.7% of the patients being incorrectly labeled as cognitively intact. This suggests that in the detection of KS, a higher cut-off should be used than the originally suggested cut-off for the detection of dementia in a psychiatric setting (Folstein et al., 1974). This finding is consistent with earlier research in Parkinson's and Huntington's disease that indicated that the cut-off of 23 is too low to show an adequate sensitivity for cognitive decline (Hoops et al., 2009; Gluhm et al., 2013). A negative consequence of applying a higher cut-off value could however be an increased likelihood for false positive results. Earlier research indicated for example that a higher cut-off value for the MMSE would result in an unacceptably low specificity in the detection of cognitive dysfunction following stroke, hereby compromising the usefulness of this screening instrument (Nys et al., 2006). It is important to notice that the base rate of KS was 50% in the current sample. If the base rate of Korsakoff's syndrome had been much lower, the PPV would decrease and NPV would increase, resulting in an increased likelihood for false positives (Ioannidis, 2005). The implication of this finding is that the PPV and NPV should be interpreted with caution in clinical settings with base rates lower than 50%.

In the current study, the correlation coefficient between the total scores of the MoCA and MMSE was high, suggesting convergent validity. The correlational analyses also showed that in patients the MMSE was not related to premorbid intellectual functioning, although it was in controls. In fact, 28.1% of the variance on the MMSE in controls was explained by the premorbid IQ estimate. This finding could reflect that for all levels of premorbid intellectual functioning, KS is associated with comparable cognitive deficits irrespective of functioning before onset of the disease. An earlier study in dementia reflected a comparable loss of association between intellectual functioning and MMSE in the progression from healthy aging to dementia, suggesting that severe neurocognitive disorders could mask the relationship between premorbid intellectual functioning and cognition (Alves, Simões, Martins, Freitas, & Santana, 2013). In the current study, the scores on the MoCA were positively related to the level of education in controls but not in patients. Earlier studies already reflected that despite the standardized correction of the MoCA score for persons with 12 years of education or less, educational level does still relate to the MoCA scores, with lower education levels often leading to lower MoCA scores (Lee et al., 2008; Kaya et al., 2014). Since this relationship between education and cognition is not reflected in KS patients, it could be suggested that the cognitive symptoms in KS are irrespective of educational level. It has to be noted that the correlation coefficients should be interpreted with caution, since the number of participants was rather small. Therefore, the specific relationship between the level of education, intellectual- and cognitive functioning in KS warrants future investigation.

The strengths of the current study include the relatively large sample size of KS patients and the stringent matching criteria between KS patients and healthy controls. This study rigorously selected patients without any co-morbid neurological or other psychiatric disorder. The demographic variables and clinical characteristics are comparable to the general build-up of the KS population (Kopelman, 2002; Wester et al., 2013). Moreover, all included KS patients had been abstinent for at least six months, minimizing the influence of alcohol related cognitive decline. A limitation of the current study concerns the homogeneity of the KS patients; all patients were inpatients of long-term care clinic for KS patients weakening possible generalizations to the acute state of KS. The MoCA and MMSE have adequate psychometric properties but it should be stressed that brief cognitive screening instruments are a poor substitute for comprehensive neuropsychological assessments, since extensive assessment covers a wide range of additional neuropsychological domains that are not included in screening instruments (Wester et al., 2013; Goldstein, & Naglieri, 2014).

In conclusion, given the high prevalence of KS in chronic alcoholics, early and routine screening for cognitive impairment with a brief, sensitive instrument is warranted. This is the first study that investigated the psychometric properties and discriminant validity of the MMSE and compared the performance on the MMSE and MoCA in KS. The results for the MoCA were systematically superior to the results for the MMSE. The MoCA was confirmed as a valid, sensitive and accurate instrument for the brief cognitive assessment in patients with KS.

Chapter 4

Quality of life of patients with Korsakoff's syndrome and patients with dementia: a cross-sectional study.

Published as:
Oudman, E., & Zwart, E. (2012). Quality of life of patients with Korsakoff's syndrome and patients with dementia: a cross-sectional study. *Journal of the American Medical Directors Association, 13, 778-781. DOI:* 10.1016/j.jamda.2012.08.003

Author Contributions: Both contributing authors designed the research and wrote the paper, E.O. conducted the experiment, planned the data analysis and performed the data analysis.

Abstract

Objectives - Korsakoff's syndrome (KS) is a chronic disorder caused by thiamine (vitamin B1) deficiency and alcoholism. The disorder is characterized by severe amnesia and often compared with dementia. The purpose of this study was to compare the quality of life between patients with KS and patients with dementia from the same nursing homes.

Design - Cross-sectional retrospective study design.

Participants - Participants were 72 patients diagnosed with KS and 75 patients diagnosed with dementia through extensive neuropsychological evaluation and multidisciplinary diagnostics.

Measurements - Quality of life (QoL) was scored with the QUALIDEM scale. Multivariate linear regression analysis was used to compare QoL between patients with KS and patients with dementia, applying the covariates "age," "gender," and "nursing home."

Results - Of the 147 included patients, 72 (48.9%) were diagnosed with KS. Patients with KS scored better than patients with dementia on the QUALIDEM subscales "Restless tense behavior," "Social relations," and "Having something to do." A trend toward a better score was found for the subscale "Positive affect"; a trend toward a lower score was found for "Feeling at home."

Conclusions - KS is associated with profound differences in QoL compared with dementia. Patients with KS tend to have more social relationships and more positive emotions than patients with dementia. Furthermore, patients with dementia show more restless behavior than patients with KS; however, patients with KS tend to feel less at home in a nursing home than patients with dementia. Results suggest that both patients with dementia and patients with KS are in need of specialized nursing homes and care programs to accomplish their specific needs.

Introduction

Korsakoff's syndrome (KS) is a chronic brain disorder caused by alcoholism and thiamine (vitamin B1) deficiency. KS is characterized by severe anterograde and to a lesser extent retrograde amnesia for declarative knowledge (Squire et al., 1982; Kopelman, 1995; Paller et al., 1997; Kopelman, 2002; Fujiwara et al., 2008; Kopelman et al., 2009). Commonly but not necessarily executive deficits are also present (eg, problems with planning, perseverations, anosognosia) (Joyce & Robbins, 1991; van Oort & Kessels, 2008; Wijnia & Goossensen, 2010). Because KS often develops in self-neglecting alcoholics, additional somatic disorders are frequently present (eg, cardiovascular disease, cirrhosis, gastrointestinal complications) (Sechi & Serra, 2007). The prevalence of KS in the general population lies between 0.04% and 2.10% (Harper, et al., 1989; Harper et al., 1998; Ramayya & Jauhar, 1997). Importantly, the prevalence of neuropathology specific to KS in alcoholics is between 12% and 15% (Zahr et al., 2011; Kril & Harper, 2012). The incidence of KS has been reported to be rising in The Netherlands and other European countries (Ramayya & Jauhar, 1997). Patients with KS are often in need of lifelong care in specialized complex care facilities, but are regularly hard to discharge from hospitals (Kok, 1991; Popoola, Keating, Cassidy, 2008). Although dementia services are generally not acquainted with KS, a fair number of patients with KS live in regular nursing homes. Here they are known to be more agitated, aggressive, and disinhibited than patients with forms of dementia (Ganzevles, De Geus, Wester, 1994). In the 1990s, specialized facilities for patients with KS demonstrated beneficial effects for both social and cognitive functioning of patients with KS compared with regular nursing homes (Ganzevles et al., 1994; Ferran et al, 1996; Blansjaar, Takens, Zwinderman, 1992). Recently, two care programs for clinical and ambulant practice of KS were developed in The Netherlands, but neither have been evaluated (de Lange, Meertens, Smits, 2001; Goossensen, Arts, Beltman, 2007). To our knowledge, systematic reports on social and emotional functioning or well-being in KS are not available. Quality of Life (QoL) is often used as a term for general well-being of individuals (Ettema, Dröes, de Lange, Mellenbergh, Ribbe, 2005a; Ettema, de Lange, Droës, 2005b). Although the number of patients with KS seems to be growing, very little is known about the QoL in KS. Most of the current knowledge is based on dementia care. The aim of the present study was therefore to compare different aspects of QoL in patients with KS and compare this with patients with dementia from the same care facilities, to increase understanding of social and emotional well-being in KS.

Methods

Setting and Study Design

A retrospective cross-sectional design was used to compare QoL in patients with KS and patients with dementia. Patient data was gathered in routine clinical care. The study took place between September 2011 and March 2012. Three nursing homes situated in Rotterdam, The Netherlands, participated in this study.

Participants

In each nursing home, patients were included in the dementia group or KS group based on diagnosis. Seventy-two patients diagnosed with KS participated in this study (62 male) and 75 patients diagnosed with dementia (26 male) participated in this study. All patients with KS fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for alcohol-induced persisting amnestic disorder and the criteria for KS described by Kopelman (Oslin, Atkinson, Smith, Hendrie, 1998; APA, 2000; Kopelman, 2002). The amnestic syndrome was confirmed by neuropsychological testing. All patients were in the chronic, amnestic stage of the syndrome. Patients with known brain abnormalities that are at odds with the diagnosis KS (ie, stroke, tumor) were not included in the analysis. Patients with unknown diagnosis or terminally ill patients were excluded. All patients with KS had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts. Diagnosis of dementia was based on diagnosis mentioned in the medical record. The Reisberg Global Deterioration Scale (GDS) is developed for assessment of primary degenerative dementia and delineation of its stages using 7 categories, 1 for no cognitive impairment and 7 for very severe cognitive decline (Reisberg, Ferris, De Leon, Crook, 1982). All patients with dementia fulfilled the criteria for stage 4 or higher according to the GDS.

Assessment Instruments

The QUALIDEM is a reliable and well-validated QoL instrument specifically developed for patients with mild to advanced dementia in residential settings and is currently the most appropriate instrument for evaluating QoL in patients with cognitive disorders who are not able to self-report (Ettema et al., 2005a; Ettema et al., 2005b; Ettema et al., 2007a; Ettema et al., 2007b; Schölzel-Dorenbos, et al., 2007; Bouman et al., 2011). The multidimensional behavior observation scale contains 37 items allocated to 9 subscales that were rated on internal consistency with Cronbach's alpha: "care relationship" (7 items, Cronbach's alpha 0.83), "positive affect" (6 items, Cronbach's alpha 0.89), "negative affect" (3 items, Cronbach's alpha 0.71), "restlessness tense behavior" (3 items, Cronbach's alpha 0.74), "positive self-image" (3 items, Cronbach's alpha 0.64), "social relations" (6 items, Cronbach's alpha 0.80), "social isolation" (3 items, Cronbach's alpha 0.59), "feeling at home" (4 items, Cronbach's alpha 0.73), and "having something to do" (2 items, Cronbach's alpha 0.62) (Ettema et al., 2007a; Ettema et al., 2007b; Schölzel-Dorenbos, et al., 2007; Bouman et al., 2011). During the start of the project, all members of the nursing staff were instructed on scoring the QUALIDEM based on the instruction guide. To get acquainted with the scoring system, all nurses had the possibility to discuss the scoring method with a psychologist, a social worker, or a nurse practitioner. The nursing staff was instructed to score the 37 items of the QUALIDEM on a 4-point scale (never, seldom, sometimes, and often) with 2 nurses on 1 score sheet to maintain a higher interobserver reliability, after observing the participant for 2 weeks. The score on each subscale was linearly transformed from 0 to 100, such that higher scores reflect a better QoL (Ettema et al., 2007a; Ettema et al., 2007b). The scores on all subscales were then averaged to reflect a general parameter for QoL. The following data were obtained from the medical record: general patient characteristics (eg, age, sex, location) and the medical history, including diagnosis of dementia or KS.

Data Analysis

Differences between patients with KS and dementia were tested using t test for interval and ratio data. A 2-tailed P value less than .05 was considered statistically significant. Univariate and multivariate linear regression was applied to investigate the difference in QoL between KS and dementia, taking into account age, sex, and location as potential confounders. Covariates were included in the regression model when there was significant evidence for differences between the KS and dementia group for the specific covariate. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL).

Results

Baseline Demographics

Of the 153 patients who were admitted to the nursing homes following the criteria as presented in the method section, 6 had missing QUALIDEM scores, so that the data of 147 patients were analyzed, 72 (48.9%) of whom had KS. The patients with dementia were older (mean age 79.1 [SD 10.2] versus 61.1 [SD 8.2]) than the patients with KS ($P < .001$). Furthermore, the dementia group consisted of more woman (65.3%) than the KS group (13.9%) ($P < .001$). The dementia group consisted of 26.6% of patients with Alzheimer dementia, 17.3% with vascular dementia, 9.3% with subcortical dementia, 4.0% with frontotemporal dementia, 34.6% with mixed etiology, and 8.0% with dementia not otherwise specified.

Quality of Life

The overall QoL in the sample was moderate (see Table 1 for statistics). A significant difference in QoL of patients with KS and patients with dementia was found without correction ($P < .001$) and with correction for age, gender, and nursing home ($P = .02$). The highest score was found on "Positive self image" and the lowest on "Having something to do." Patients with KS scored significantly lower than patients with dementia on 2 of the 9 QUALIDEM subscales, namely "Feeling at home" and "Care relationship." Patients with KS scored significantly better on 4 of the 9 QUALIDEM subscales, namely "Restless tense behavior," "Social relations," "Negative affect," and "Having something to do" (Table 1). The characteristics of age, gender, and nursing home changed the differences between KS and dementia. After adjustment for these factors, the difference in "Care relationship" and "Negative affect" between patients with KS and patients with dementia was no longer significant. The difference in "Positive affect" and "Feeling at home" showed a trend toward significance for differences between the KS and dementia group.

Table 1. Observed Quality of Life in dementia and Korsakoff's Syndrome.

QUALIDEM Subscales	KS (n=72) Mean Scale Score (SD)*	Dementia (n=75) Mean Scale Score (SD)*	KS versus Dementia B-Unadjusted Coefficients	95% CI for B-Unadjusted Coefficients	P Value	B-Adjusted CoefficientsΔ	95% CI for B-Adjusted CoefficientsΔ	P Value
Care relationship	55.2 (21.9)	68.8 (19.4)	-13.7	-20.4 - -6.9	<.01	-3.8	-14.1 - 6.6	.47
Positive affect	70.0 (22.4)	67.3 (21.0)	2.7	-4.4 - 9.8	.45	10.1	-1.0 -21.2	.07
Negative affect	72.8 (21.2)	64.3 (28.6)	8.5	0.3 - 16.8	.04	-2.4	-14.7 - 9.8	.70
Restless tense behavior	68.9 (33.7)	50.8 (32.4)	18.1	7.3 - 28.8	<.01	22.4	-5.5 - 39.2	.01
Positive self image	82.6 (21.2)	80.3 (23.6)	2.3	-5.1 - 9.6	.54	-8.0	-19.3 - 3.3	.17
Social relations	63.3 (23.3)	50.1 (19.4)	13.3	6.3 - 20.3	<.01	13.9	3.1 - 24.8	.01
Social isolation	69.9 (20.4)	67.7 (22.8)	2.2	-4.9 - 9.3	.54	0.1	-10.8 - 11.0	.98
Feeling at home	63.2 (27.0)	78.9 (25.0)	-15.7	-24.2 - -7.2	<.01	-13.1	-26.4 - 0.3	.06
Having something to do	55.1 (33.8)	20.4 (26.5)	34.6	24.8 - 44.5	<.01	27.2	11.8 - 42.6	<.01

KS, Korsakoff's Syndrome; CI, confidence interval; SD, standard deviation; n = number. * QUALIDEM mean scale scores range: 0-100, higher scores indicate a better quality of life. Δ All outcome variables are adjusted for age, gender and nursing home.

Discussion

To our knowledge, this is the first study that investigated QoL in patients with KS and compared this with QoL of patients with dementia. Because it is difficult to evaluate QoL in patients with severe cognitive deficits, we used the QUALIDEM, an assessment tool for QoL in patients with dementia. The QoL for the participants in the current study suggest a better QoL in KS compared with dementia, with profound differences between both groups. Overall QoL was moderate, with mean subscale scores lower than 70%. Patients with KS scored better than patients with dementia on the QUALIDEM subscales "Restless tense behavior," "Social relations," and "Having something to do" after correction for age, gender, and nursing home. Moreover, a trend toward a better score was found for the subscale "Positive affect" and a trend toward a lower score was found for "Feeling at home."

Restless tense behavior is one of the core features of dementia that often appear at twilight. This phenomenon is referred to as "sundowning." and has been associated with a dysregulation of the suprachiasmatic nucleus (SN) (Bliwise, et al., 1993; Burney-Puckett, 1996). Recent research shows that ambient bright light reduces restless behavior in dementia, supporting the role of the SN in restless behavior (Riemersma-van der Lek, 2008; van Hoof et al., 2009). As far as we know, KS has not been associated with dysregulation of the SN. This could have resulted in lower scores of patients with dementia on the QUALIDEM subscale that quantifies restless behavior compared with patients with KS. Although an earlier study showed evidence for more agitated, aggressive, and disinhibited behavior than patients with forms of dementia (Ferran et al., 1996), the current study found evidence that patients with KS have more social relations than patients with dementia. A possible explanation for this finding is that a large number of patients with dementia have cognitive deficits extending into more cognitive domains than KS (Kok, 1991). Patients with KS and patients with dementia both show clear deficits in memory. Moreover, commonly patients with KS and patients with dementia show executive dysfunctions (Joyce & Robbins, 1991; van Oort & Kessels, 2008; Wijnia & Goossensen, 2010) whereas dementia is also known for apraxis, aphasia, agnosia, and disorders in attention (Oslin et al., 1998). Cognitive disorders are likely to reduce the possibility to engage in social relationships.

Our study found evidence for a tendency toward significant differences in positive emotions between patients with dementia and patients with KS, with the KS group showing more positive emotions. As vascular dementia and subcortical dementia progressively flattens mimicry and renders individuals unable to express emotions, the ability to measure affect in these patients may be reduced (Riemersma-van der Lek, 2008). Moreover, Alzheimer dementia is known for progressive problems in emotion processing (Cadieux & Greve, 1997). Earlier research indicated that KS does not necessarily involve flattening of affect or other emotional abnormalities, which might explain the results in the current study (Douglas & Wilkinson, 1993)); however, we recommend more research into the expression of positive emotions in KS.

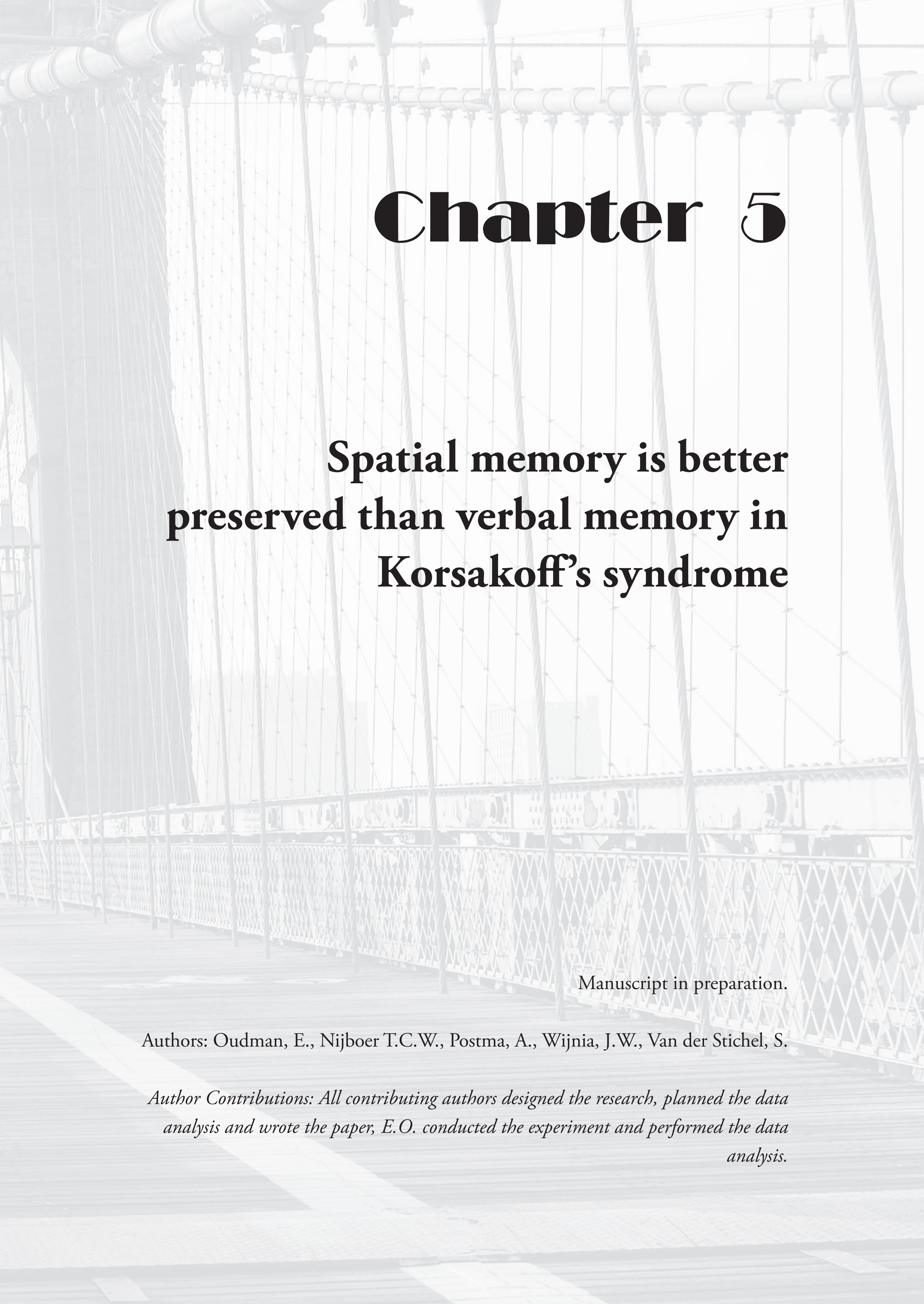
Our study showed that the general QoL is higher in KS than in dementia, with a very different profile on QUALIDEM subscales. This finding supports the idea that both patient groups are in need of different types of care. Recent care programs suggest that patients with KS are in need of accompaniment and structure, whereas patients with dementia are more in need of empathy and understanding (de Lange et al., 2001; Goossens et al., 2007). The need for structure in KS is likely to coincide with the executive deficits that are common in KS (Joyce & Robbins, 1991; van Oort & Kessels, 2008; Wijnia & Goossensen, 2010).

This study has some limitations. The cross-sectional design means that we could not draw any conclusions about the causality between QoL and diagnosis. Moreover, the participants in the dementia group were significantly older and the group consisted of a higher proportion of women. QoL is known to be negatively affected by aging through limitations in mobility, long-standing illness, and difficulties with everyday activities (Kemp & Ettelson, 2001; Netuveli et al., 2006). Furthermore, both women and men have a differential way of coping with aging (Quick & Moen, 1998; Emery et al., 2004). We tried to correct for possible confounders, however, by adding age, gender, and nursing home as covariates to the model. As far as we suggest, any other confounding characteristic could not explain the differences between both research groups. Nevertheless, it would be of great relevance to perform a study to compare the QoL in patients with KS with an age- and gender-matched control group of patients with dementia. Since the current article forms an initial starting point into the investigation of QoL in KS, we encourage more research on QoL in KS with supplementary measurements of QoL and well-being. Unfortunately, no information was available on the patients, premorbid intelligence or level of education in our study.

Furthermore, the current study did not correct for different stages of dementia, nor for severity of the KS syndrome; however, recent evidence suggests no evidence for differences in QoL between more advanced stages of dementia or early dementia (Schouten et al., 2012).

Conclusion and Recommendation

This study demonstrates profound differences in QoL between patients diagnosed with dementia and patients with KS. Average QoL was higher in KS than in dementia. Patients with KS tend to have more social relationships and more positive emotions than patients with dementia. Furthermore, patients with dementia show more restless behavior than patients with KS. We suggest that differences between both patient groups could be explained by differences in cognitive deficits. For example, KS is known for profound amnesia and frequently also executive deficits, which require structure and scheduled day programs. For this reason, we recommend specialized nursing homes and care programs for patients with KS to accomplish their specific needs.



Chapter 5

Spatial memory is better preserved than verbal memory in Korsakoff's syndrome

Manuscript in preparation.

Authors: Oudman, E., Nijboer T.C.W., Postma, A., Wijnia, J.W., Van der Stichel, S.

Author Contributions: All contributing authors designed the research, planned the data analysis and wrote the paper, E.O. conducted the experiment and performed the data analysis.

Abstract

Korsakoff's syndrome (KS) is a neuropsychiatric disorder characterised by anterograde declarative amnesia, which is caused by thiamine deficiency and concomitant alcoholism. While the presence of severe impairments in declarative memory in KS has long been acknowledged, the precise characteristics of these memory deficits need further investigation. In declarative memory, two relevant distinctions reflect the required operations and the content that needs to be memorized. The aim of the present study was twofold: to investigate whether patients diagnosed with KS have larger difficulties in working memory, long term memory encoding or long term memory recall operations, and whether these memory difficulties are most pronounced for verbal or spatial memory content. Normed performance on six neuropsychological indices of declarative memory was compared in 25 patients diagnosed with KS. The results demonstrated that patients with KS have compromised memory functioning on all memory indices compared to normed performance. Importantly, spatial memory performance was relatively better preserved than verbal memory. Task performance was specifically lower in the encoding operation compared to the working memory operation and delayed recall operation. There was no interaction between memory content and operation of processing, suggesting that memory operations are compromised irrespective of memory content. The results of this study suggest that when cued-recall of information is possible such as in the spatial tasks, memory performance in KS might profit.

Introduction

Korsakoff's syndrome (KS) is a neuropsychiatric disorder characterised by anterograde declarative amnesia, which is caused by thiamine deficiency and concomitant alcoholism. In KS, declarative memory is affected to a more extreme extent than other cognitive functions (Kopelman, 2002). What is yet less known is whether all declarative memory components are impaired to the same extent in KS. Two relevant distinctions can be made in declarative memory: the distinction in terms of cognitive operations (including accessibility, storage and temporal properties) and the distinction between content that needs to be memorized. Although declarative memory deficits in KS have received considerable attention in the literature, it remains largely unknown whether the deficits involve all declarative memory operations or are restricted to demarcated subforms. There is various evidence that working memory, which holds and operates on information for a brief period, is less compromised than long term memory encoding and recall in KS (Cermak, Butters, Goodglass, 1971; Haxby, Lundgrun, and Morley, 1983; Kopelman, 1991; Joyce & Robbins, 1991; Mayes, Daum, Markowisch, Sauter, 1997; Squire, 2009). Deficits in working memory, if any, would specifically involve the transition between working memory and long term memory encoding, which has also been referred to as the "episodic buffer" (Baddeley, 2001; Van Asselen et al., 2005; Oudman et al., 2011). Additionally, deficits in long term memory and recall are suggested to be unrelated to working memory deficits (Oscar-Berman et al. 1992; Van Geldorp et al., 2012). Also regarding long term memory itself, it is largely unclear whether deficits in encoding or recall are most pronounced. Recently, some studies found evidence that problems in declarative memory recall are likely to be more characteristic for KS than encoding deficits, although also declarative memory encoding deficits have been reported in KS (Van Damme & d'Ydewalle, 2008; Oscar-Berman, 2012; Kopelman, 2009). Since it is still debated whether the declarative memory deficits in KS involve all operations, one of the central aims of this study was to directly compare working memory, long term memory encoding, and long term memory recall operations in patients diagnosed with KS.

A second question regarding the memory difficulties in KS was whether declarative memory problems in KS generalize to all *contents*. In working memory literature a typical content distinction is that between verbal and visuospatial (Baddeley & Hitch, 1974). Spatial memory refers to the memory for the place an event occurs, while verbal memory involves the interpretation and recollection of words, digits and amodal linguistic units. Over years, a substantial amount of studies has demonstrated evidence for severely compromised spatial memory in KS (see Kessels & Kopelman, 2012 for a review). Patients with KS have pronounced problems in remembering exact and relative object locations (Chalfonte et al., 1996; Kessels, Postma, Wester, de Haan, 2000). Moreover, forming associations between temporal order memory and spatial memory is even more deficient (Postma, Van Asselen, Keuper, Wester, & Kessels, 2006). Parallel to the evidence that spatial memory deficits are considerable, there are also multiple studies that demonstrate vastly diminished verbal memory functioning. Patients diagnosed with KS have impaired immediate recall, flat learning rates across learning trials, and poor retention over delay intervals on indices of verbal memory compared to healthy controls (Butters, Wolfe, Granholm, Martone, 1986; Pitel, Beaunieux, Witkowski, Vabret, de la Sayette, Viader, Desgranges & Eustache, 2008).

To our knowledge, no direct comparisons between declarative memory operations and content have yet been attempted in KS. Therefore, the aim of the present study was twofold: to investigate whether patients diagnosed with KS have stronger difficulties in working memory, long term memory encoding or long term memory recall operations, and whether these memory difficulties are most pronounced in verbal or spatial memory content. Task performance in a group of KS patients was compared to the normed reference group task performance on two well-known verbal and two spatial neuropsychological tests for declarative memory, leading to indices for working memory, long term memory encoding and long term memory recall in both the spatial and verbal content domain. For the working memory operation, those indices included the Digit Span (DS) for verbal working memory and the Corsi Block Tapping Test (CBT) as a spatial counterpart. For long term memory encoding, those indices included the summed learning trials of the Rey's Verbal Memory Test (RVMT) for verbal long term encoding and the summed learning trials for the LLT as a spatial equivalent. Finally, for long term memory recall, those indices included the delayed recall in the RVMT for verbal long term memory recall and for the LLT as an index for spatial long term memory recall. Following the context memory deficit hypothesis, contextual memory is thought to be disproportionally compromised in KS compared to the memory itself (Mayes, Meudell, & MacDonald, 1991). Based on this hypothesis it can be speculated that spatial memory performance, one of the most important forms of contextual memory, would be more compromised than verbal memory performance.

Methods

Participants

Twenty-five patients (mean age = 58.8; SD = 7.3), diagnosed with KS participated in this study. The patients were inpatients of the Korsakoff Center, "Slingedael", Rotterdam, The Netherlands. All patients fulfilled the DSM-V criteria for substance/medication induced major neurocognitive disorder (American Psychiatric Association, 2013), and the criteria for KS described by Kopelman (2002). The amnestic syndrome with severe anterograde amnesia was confirmed by neuropsychological assessment. All patients were in the chronic stage of the syndrome, and none were in the confusional Wernicke delirium at time of testing. Premorbid IQ was estimated with the Dutch Adult Reading Test (Schmand, Lindeboom, & Van Harskamp, 1992), which is the Dutch version of the National Adult Reading Test. All included patients had an estimated IQ score above 80, to exclude patients with low intellectual or cognitive functioning interfering with the testing procedure, possibly caused by alcohol dementia (mean IQ = 94.4; SD = 10.4) (Oslin, Atkinson, Smith, & Hendrie, 1998). General cognitive functioning was assessed with the Mini Mental State Examination (mean score: 23.6; SD: 2.8) (MMSE; Folstein, Folstein, & McHugh, 1975). All patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts. Selected patients did not show neurological disorders (Traumatic Brain Injury, epilepsy, etc.) or acute psychiatric conditions (psychosis, major depression, etc.) interfering with the testing procedure.

Materials

Verbal Working Memory - Digit Span

The forward verbal working memory span is a verbal index of short-term memory or working memory (Lezak, 1995; Salamé et al., 1998) and was calculated with the Digit Span subtest from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997). Percentile scores for digit span were calculated based on recently available norms (n=362; Monaco, Costa, Caltagirone, Carlesimo, 2013), as an index for verbal working memory.

Spatial Working Memory - Corsi Block Tapping Span

Patients were administered the Corsi Block Tapping Test to index spatial working memory. The spatial span of the Corsi Block Tapping Test is a span task and, as such, a visuospatial analogue to the digit span as an index of verbal short-term memory or working memory (Lezak, 1995; Kessels, van Zandvoort, Postma, Kappelle, De Haan, 2000). Percentile scores for the forward spatial span were calculated based on recently available norms (n=362; Monaco, Costa, Caltagirone, Carlesimo, 2013), as an index for spatial working memory.

Verbal Long Term Memory - Rey's Verbal Memory Test

Rey's Verbal Memory Test (RVMT; Rey, 1958) was developed to measure impairments in encoding and recall of verbal information in patients with acquired brain damage. In the RVMT, fifteen monosyllabic words are presented in five subsequent trials, with a free recall procedure immediately following each presentation. After a delay of about 20 minutes, there is an additional delayed free recall trial, followed by a recognition trial. The Dutch version (Brand & Jolles, 1985) was used in the current study. For the total score for the five subsequent trials and the delayed free recall trial, percentile scores were calculated based on the most recent available norms for the Dutch population (n=847; Schmand, Houx, de Koning, 2012). The percentile scores on the five subsequent trials were used as an outcome measure for verbal long term memory encoding, and the percentile scores on the delayed free recall (relative delayed free recall to learning phase) were used as an outcome measure for verbal long term memory recall.

Spatial Long Term Memory - Location Learning Test

The Location Learning Test was administered to examine spatial memory. This test was developed by Bucks and Willison (1997) and later slightly modified by Kessels, Nys, Brands, Van den Berg, & Van Zandvoort (2006). The LLT consists of a 40 × 40 cm board on which 10 gray-scaled pictures of easy to name objects (boot, wallet, umbrella, book, envelope, knife, cup, glasses, matches, and scissors) were placed at different locations in a 5 × 5 grid. In the current experiment, each trial the board was presented for 30 seconds (procedure I), after which cards of the ten objects had to be relocated as accurately as possible on an empty 5 × 5 grid with the same dimensions as the board with the 10 gray-scaled pictures. After five learning trials, in which the same stimulus was shown, delayed recall was tested after 15 minutes. For each of the five learning trials and the delayed trial, the displacement score was determined, that is, the sum of the errors made for each object placement on that trial. A placement error was calculated by counting the number of cells the object had to be moved both horizontally and vertically to be in the correct location (Kessels, Bucks, Wilison, Byrne, 2012). The displacement score reflects the ability to bind objects to their locations in memory.

For the total score for the five subsequent trials and the delayed free recall trial, percentile scores were calculated based on the most recently available norms (n=186; Kessels, Bucks, Wilison, Byrne, 2012). The percentile scores on the five subsequent trials were used as an outcome measure for spatial long term memory encoding, and the percentile scores on the delayed free recall trial (relative delayed free recall to learning phase) were used as an outcome measure for spatial long term memory recall.

Analysis

In the statistical analysis, the indices for verbal working memory and spatial working memory are referred to as "*working memory operation*". Moreover, the indices for verbal long term encoding and spatial long term encoding are referred to as *"encoding operation"* in the statistical analysis. The indices for verbal long term memory recall and spatial long term memory recall are referred to as *"recall operation"*. A 2 × 3 ANOVA with 'content' (spatial and verbal) and 'operation' (working memory operation, encoding operation and recall operation) as within-group factors was performed. Additionally, Bonferroni corrected pairwise comparisons were performed to further specify whether there were significant differences between the operations (working memory operation, learning operation and delayed recall operation). To further elaborate the relationship between declarative memory 'content' (spatial and verbal) and 'operation' (working memory operation, encoding operation, and delayed recall operation), a Pearson's correlation coefficients (r, two-tailed) were reported.

Results

Figure 1 depicts box-plots of percentile scores for the working memory operation, the encoding operation and the recall operation of the spatial and verbal memory tasks in patients with KS. A one sample *t* test was conducted on all declarative memory indices, to evaluate whether their mean was significantly different from the average percentile score in the normative group (see the reference line in Figure 1). All reported KS patient group scores on indices of declarative memory were lower than the normative group (*ps* < .01), suggesting that declarative memory performance was compromised in KS compared to a normative reference group.

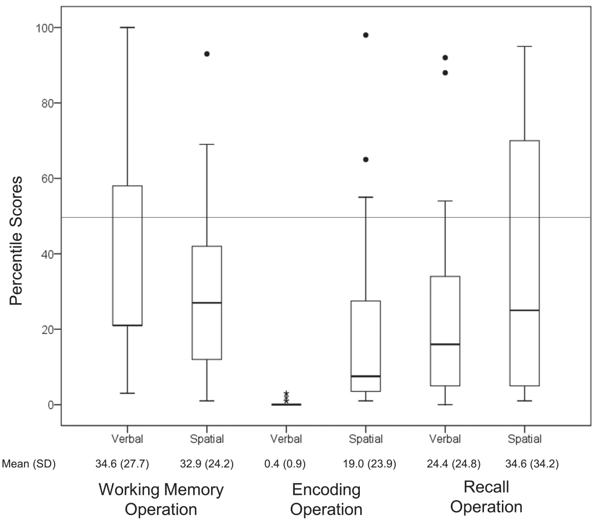


Figure 1. Box-plot percentile scores for the working memory operation, the encoding operation and the recall operation on the verbal and spatial declarative memory tasks in patients with KS. The reference bar is the average percentile score in the normed reference groups.

A main effect of content was observed ($F(1,24) = 11.1$, $p < .01$, $\eta_p^2 = .316$), indicating that normed task performance in KS patients was better on the spatial memory tasks than the verbal memory tasks. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated for operation. Therefore, we used Greenhouse–Geisser-corrected values for the ANOVA of this variable. A main effect was found for operation ($F(1.5,37.2) = 11.8$, $p < .0001$, $\eta_p^2 = .329$), indicating differences in normed task performance between working memory, encoding and recall operations. No significant interaction between content and operation was observed ($F(2,48) = 2.0$, $p = .147$, $\eta_p^2 = .077$), suggesting that for both the verbal and spatial content the profile of scores was comparable for each memory operation.

Post hoc analysis indicated that performance was specifically lower in the encoding operation, compared with the working memory operation (Mean difference: 24.0, percentile points, p<0.001) and recall operation (Mean difference: 19.8, percentile points, p < 0.001). Performance in the working memory operation was comparable with the performance in the recall operation (Mean difference: 4.2 percentile points, p = 1).

Correlations between test results

Table 1. Correlation matrix for the percentile scores for the declarative memory indices (n=25).

	Verbal Working Memory	Spatial Working Memory	Verbal Encoding	Spatial Encoding	Verbal Recall
Verbal Working Memory					
Spatial Working Memory	.08				
Verbal Encoding	.23	-.22			
Spatial Encoding	.01	-.24	-.05		
Verbal Recall	-.32	.07	-.40*	.49*	
Spatial Recall	.10	-.22	.14	.29	.28

Note. *= significance at p<.05.

As described, we observed relatively better preserved spatial than verbal content memory performance in KS. Moreover, there were differences in normed task performance between working memory, encoding and recall operations. To further elaborate the relationship between memory content and memory operation, we performed additional correlations on the declarative memory scores. Pearson's correlations are reported in Table 1. The correlations show that spatial encoding and verbal recall correlated positively, suggesting that despite the differential content of declarative memory, declarative memory operations in KS are interrelated. Moreover, verbal encoding and recall were negatively correlated. This finding is harder to interpret and is further dealt with in the discussion.

Discussion

The aim of the present study was twofold: first to investigate whether patients diagnosed with KS have stronger verbal or spatial memory difficulties on neuropsychological memory tests and second to determine whether these memory difficulties are more pronounced in working memory, long term encoding or recall. The results of the present study show that task performance in patients with KS was significantly lower than in the normed reference groups on all indices of declarative memory functioning. Results also indicated that spatial memory was relatively better preserved in KS than verbal memory. Performance was hampered in the long term memory encoding operation, compared to the working memory and recall operation, suggesting that independent of memory content the long term encoding of information is most severely diminished in KS. Importantly there was no interaction between memory content and operation in patients diagnosed with KS, suggesting that irrespective of content, memory operations in KS are severely compromised.

Earlier studies have already indicated that patients with KS have severe global deficits in their declarative memory functioning (see Kopelman, 2009 for a review). The findings of this study extend this observation by showing a marked pattern of declarative memory deficiencies over memory operations, with the most severe problems in memory encoding. Following the context-memory deficit hypothesis, contextual memory is thought to be disproportionally compromised compared to target memory (Mayes, Meudell, & MacDonald, 1991). As such one would expect greater memory deficits for spatial information. However, in the current study spatial memory was better preserved than verbal memory. The results of the present study thus seem to contradict the context memory deficit hypothesis at first sight. A possible explanation might be that the current spatial memory tasks (LLT and CBT) have response alternatives (i.e. locations) that are more restricted than in the RVMT and DS (i.e. words or digits to be freely produced). As such, these tasks can be considered to have more a cued recall format. Also implicit, nondeclarative factors could have helped performance in the LLT. Placing one object in the correct location could work as an implicit cue for subsequent objects. It is important to note that many real-life situations that require object-location memory involve some form of cued-recall instead of complete free recall. For example, if we need to find our keys in a crowded living room, we are likely to start searching in the right direction cued by the spatial aspects of our living room (Postma et al., 2008; Oudman et al., 2011, Oudman et al., 2014). Although the cued recall format resembles real-life situations, it would be relevant in future studies to match verbal and spatial memory closer on free and cued-recall aspects.

A likely consequence of the cued recall property of the LLT is that overall the task is easier to perform than its verbal equivalent. Earlier research on the LLT revealed that this task is prone to ceiling effects in a healthy population and the learning phase of the LLT should be accelerated to overcome this problem (Kessels et al., 2006). It is nevertheless of interest to see that patients diagnosed with severe memory problems, due to KS, are capable of learning object-locations despite their severe amnesia.

Another notable feature of the LLT is that it foremostly assesses categorical spatial processing. Previous work has underscored the difference between categorical and coordinate space processing (Van Asselen, Kessels, Kappelle, Postma, 2008; Postma, Kessels, Van Asselen, 2008). Categorical space processing refers to relative object to location binding, while coordinate space processing refers to the exact locations of objects in space. In the LLT, the objects are presented relative to other objects and a reference frame. In the work by Van Asselen and colleagues (2008) object locations are presented in free space, requiring more 'metric' recall of locations. In light of these considerations future studies should disentangle categorical and coordinate spatial learning in KS and investigate whether coordinate spatial learning is also better preserved than verbal learning.

Of secondary interest we computed correlations between memory operations scores and between memory contents scores. Admittedly, because of the relatively small sample size the lack of significant correlations should not be given too much weight. In this study, verbal encoding and recall were negatively correlated. A possible explanation for this remarkable finding is that the percentile scores for long term recall are corrected for the number of items that are encoded. This negative correlation is therefore likely to reflect an artifact, instead of an actual negative relationship between encoding and recall. Of more interest, spatial encoding and verbal recall correlated moderately positive. This result shows that better spatial encoding performance was related to a verbal recall advantage, and suggests that both memory operations and content are interrelated to some extent despite the lack of significant interaction between memory operations and content.

Strengths and limitations

One of the strengths in the current study is the design that included both memory operations and content in KS. To our knowledge, there were no such studies available. Moreover, this is the first report on the LLT in KS patients, finding evidence for preserved learning potential during the encoding of locations. There are also some methodological considerations that have to be taken into account in the interpretation of the present findings. This study was conducted with KS patients with severe amnesia that had an unquestionable diagnosis of KS and were inpatients of a clinic for chronic KS care. The results may therefore not generalize to patients that do show less pronounced memory disturbance. Moreover, the sample size of this study was small, but comparable to other studies on neuropsychological functioning in KS (Van Damme & d'Ydewalle, 2008; Postma et al., 2008). Future research might examine verbal and spatial memory and learning in larger samples of patients with KS divided in levels of amnesia severity.

Conclusion

In conclusion, patients diagnosed with KS show severe memory disorders on regular neuropsychological examination, although spatial learning and memory seem better preserved than verbal learning and memory. Based on the findings of this study it is relevant for patients with KS to increase the number of available spatial cues during the process of memory rehabilitation.

Chapter 6

Intact memory for implicit contextual information in Korsakoff's syndrome

Published as:

Oudman, E., Van der Stigchel S., Wester A.J., Kessels R.P.C., & Postma A. (2011). Intact memory for implicit contextual information in Korsakoff's amnesia. *Neuropsychologia, 49, 2848-2855. DOI:* 10.1016/j.neuropsychologia.2011.06.010

Author Contributions: All contributing authors designed the research, planned the data analysis, and wrote the paper, E.O. conducted the experiment and performed the data analysis.

Abstract

Implicit contextual learning is the ability to acquire contextual information from our surroundings with- out conscious awareness. Such contextual information facilitates the localization of objects in space. In a typical implicit contextual learning paradigm, subjects need to find a target among a number of distractors during visual search. Some of the configurations of stimuli are repeated during the experiment resulting in faster responses than for novel configurations, without subjects being aware of their rep- etition. Patients with Korsakoff's syndrome (KS) have been found to show devastating explicit spatial amnesia. Less is known about their implicit spatial memory abilities. The aim of the present research was to examine whether implicit contextual learning is intact in KS. Therefore, eighteen KS patients and twenty-two age-IQ- and education-matched controls performed the Implicit Contextual Learning task and a paradigm intended to assess explicit, spatial working memory, i.e. the Box task. Intact implicit contextual learning was observed in both the control group and the KS patients. In turn KS patients did have markedly lower explicit spatial working memory scores. The implicit learning effect was not related to the spatial working memory scores. Together these results clearly suggest that implicit and explicit spatial memory have a different neurocognitive basis.

Introduction

Korsakoff's syndrome (KS) is a chronic disorder often caused by severe alcoholism in combination with thiamine (vitamin B_1) deficiency leading to diencephalic, frontal and hippocampal brain damage. The disorder is characterized by severe anterograde and – to a lesser extent – retrograde amnesia for declarative knowledge (Squire, 1982; Kopelman, 1995; Paller et al., 1997; Kopelman, 2002; Fujiwara et al., 2008). Although the amnesia in KS patients affects all subdomains of explicit memory, there is evidence that these patients have even more pronounced problems in remembering contextual information, such as spatial memory for coordinate (exact locations of objects in space) as well as categorical (relative) object to location binding (Chalfonte et al., 1996; Kessels et al., 2000), allocentric (object-to-object relation) and egocentric (self-to-object relation) spatial memory (Holdstock et al., 1999) and forming associations between temporal order (moment) information and spatial information (Postma et al., 2006).

Most of the foregoing studies assessed explicit or conscious memory. However, it is currently unclear whether implicit memory is intact in KS. On the one hand, there is ample evidence for spared implicit memory in verbal repetition priming (Graf et al., 1985; Cermak et al., 1991), perceptual priming (d'Ydewalle & Van Damme, 2007), motor sequence learning (Nissen et al., 1989) or procedural learning (Fama et al., 2006) in KS. On the other hand, some studies did find that conceptually-driven implicit memory was hampered (Brunfaut & d'Ydewalle, 1996), perceptual priming for picture-fragment completion was impaired (Verfaellie et al., 1996), sequence learning is compromised when there is a strong spatial component (Van Tilborg et al., 2011), or suggested that intact procedural memory is the result of enhanced instructions rather than intact implicit memory processes (Swinnen et al., 2004). In the latter study procedural learning did not occur in KS without augmented feedback information being present during the learning process.

The present study investigated whether one aspect of implicit memory, namely implicit *spatial* memory, is intact in KS. In daily lives, people often make use of implicit spatial memory. We may automatically take the right turn even without having a clear sense where to go. Moreover, we may start searching in the right direction for a hidden object without a conscious place memory. Following the context-memory deficit hypothesis, all facets of the memory for the moment and place an event occurs are thought to be disproportionally disturbed in KS compared to the memory itself (Mayes et al., 1991), which suggests that implicit spatial memory is hampered in KS. Supportive for this hypothesis was a study by Verfaellie and colleagues (1992) suggesting that KS patients are less able to make use of implicit spatial memory than healthy controls if the test material could not be verbalized.

Conversely, a study by Postma and colleagues (2008) showed that during an object-location memory task, KS patients demonstrated stronger unconscious influence of previously shown spatial configurations on subsequent trials compared to healthy controls, whereas KS patients performed substantially worse on conscious object-location memory.

Given these inconsistent findings with respect to implicit spatial memory in KS, we aimed to investigate whether patients with from KS are able to implicitly learn spatial regularities despite their diffuse memory impairments. The present study adopted the implicit contextual learning paradigm (Chun & Jiang 1998; Chun, 2000). In this visual search task a target (T) has to be located among a number of distractors (L). Subjects have to indicate whether the target is rotated to the left or the right. In each session, a set of arbitrary visual contexts are generated by manipulating the spatial configuration of the target and distractors. After training, the target is found faster when configurations are repeated than novel configurations, referred to as implicit contextual learning (Chun & Jiang, 1998; Chun, 2000). This implicit aspect of this learning is supported by an awareness check, that is, when explicit recognition is tested after contextual learning, participants perform at chance level. Furthermore, when subjects were asked whether or not they observed that some contexts were repeated throughout the task, they were unaware of this (Chun & Jiang, 1998). The explanation for the learning effect is that contextual information, such as the positions of objects with respect to each other, can be used to guide our attention to a specific location after repeated rehearsal even without reaching conscious awareness. Implicit contextual learning can already be obtained after 5 or 6 repetitions, indicating that it is a fast effect (Chun and Jiang, 2003). Moreover, the effect can be also observed one week after the initial learning phase, indicating it remains in memory for a long period of time (Jiang et al., 2005).

In order to further examine the interrelations between the implicit context learning task to a more explicit spatial memory we included a spatial working memory test which also has a search component: the Box task. The Box task requires participants to search for objects that are hidden in different boxes that are shown on a screen (Van Asselen et al., 2005; Morris et al., 1987; Feigenbaum et al., 1996). It requires participants to keep spatial information in memory both over a very short time period (i.e., keeping it 'on-line') and a more extended time range (possibly marking the transfer from working memory into long term memory). By combing evidence on both an implicit and an explicit spatial tasks we wanted to elucidate possible communalities in neurocognitive basis.

Methods

Participants

Twenty-six patients diagnosed with Korsakoff's syndrome participated in this study (eighteen males). They were all inpatients of the Korsakoff clinic of the Psychiatric Hospital 'Vincent van Gogh', Venray, The Netherlands. Two male patients were excluded from analysis after dropping out during testing because of motivational problems. For all patients, the current intelligence level of each participant had to be in concordance with the estimation of premorbid functioning based on occupational and educational history to exclude cases of dementia (Oslin et al., 1998). Two patients (one male) with estimated IQ scores below 80 were excluded because of low intellectual functioning interfering with the testing procedure, possibly caused by alcohol dementia. Also, two patients (one male) with disproportionate hippocampal atrophy and two patients (two male) with additional brain infarctions were excluded.

The remaining eighteen patients (12 male) and twenty- two (13 male) age-, premorbid IQ and education matched controls were included in the analysis. All patients fulfilled the DSM-IV criteria for alcohol-induced persisting amnestic disorder (American Psychiatric Association, 2000) and the criteria for Korsakoff's syndrome described by Kopelman (2002). The amnestic syndrome was confirmed by extensive neuropsychological testing. All patients were in the chronic, amnestic stage of the syndrome, none of the patients was in the confusional Wernicke psychosis at the moment of testing. Neuroradiological examination (Magnetic Resonance Imaging for 13 participants and Computed Tomography for 4 participant) showed signs of brain atrophy and nonspecific white-matter lesions in most patients, which are often found in KS but not a necessary criterion for the diagnosis (Kopelman, 2002). No brain abnormalities were found that are at odds with the diagnosis KS (i.e., stroke, tumor). Patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts or family reports (see Table 1). All participants were administered the Dutch version of the California Verbal Learning Test (a task measuring verbal immediate and long-term memory) and scored within the first to the fifteenth percentile on the total number of List A words recalled in Trials 1-5 (standardized for age and gender). For all eighteen patients assessed with the Rivermead Behavioural Memory Task, a moderate to serious disturbance on daily memory was found (Wilson et al., 1985).

Table 1. Summary of demographic variables for all participants

Measurement	Patients	Controls	Significance
Number (number of males)	18 (12)	22 (13)	$\chi^2(1) = 0.57$, p=0.45
Handedness (R: L: R&L)[1]	14 : 3 : 1	19 : 2 : 1	$\chi^2(2) = 1.01$, p=0.60
Educational level μ (SD)[2]	4.5 (0.8)	4.6 (0.9)	U(38) = 0.85, p=0.44
Years of education μ (SD)[3]	10.1 (2.0)	10.2 (1.9)	t(38) = 0.20, p=0.84
IQ estimation μ (SD)[4]	98.1 (8.5)	102.1 (8.3)	t(38) = 1.51, p=0.14

[1] Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). [2] Educational level was assessed in 7 categories: 1: < primary school; 7 = academic degree (Verhage, 1964). [3] Years of education were calculated based on the years of education corresponding to the Dutch educational level (Hochstenbach et al., 1998). [4] IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

All participants had severe explicit memory deficits (see Table 2) as measured with the California Verbal Learning Test (CVLT) and the Rivermead Behavioural Memory Test (RBMT). Additionally, patients had intact visuospatial short-term memory span, as measured with the Corsi Block-Tapping Test (forward). The Corsi Block-Tapping Task is a standardized span task and a visuospatial analogue to the digit span as an index of verbal short-term memory (Kopelman, 1991; Kessels et al., 2000).

For both the patients and the control group education level was assessed using seven categories, 1 being the lowest (less than primary school) and 7 being the highest (academic degree) (Verhage, 1964). These categories were converted to the internationally applied classification using years of education (Hochstenbach et al., 1998). Premorbid IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992). For all participants, handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the Institutional Review Board and written informed consent was obtained in all patients. Table 2 shows a summary of demographic variables, neuropsychological test results and radiological findings for all patients.

Equipment and stimuli for the Implicit Contextual Learning Task
For the implicit contextual learning paradigm the software package Presentation (Neurobehavioral Systems) was used to present the visual search task. Eleven distractor stimuli (L) and one target stimulus (T) were presented each trial. The color of all stimuli was white on a grey background. The distractor stimuli were created to make them look similar to the target stimulus (see figure 1). The stimulus size was 0.92° × 0.92°. Target location was balanced for distance from the screen's center and screen half (left/right). Distractor stimuli could be rotated 0°, 90°, 180°, 270° and the target stimulus could be rotated 90° or 270°. The direction of rotation of the target stimulus was randomly defined, in order to prevent subjects from learning fixed stimulus–response associations. Target position were generated by randomly placing 11 distractors and 1 target in an invisible grid of 12 rows × 12 columns (144 possible positions), with individual points separated by 2.3°.

Procedure for the Implicit Contextual Learning Task
Participants were seated in a comfortable chair in front of the computer screen in a semi-darkened room. The computer screen was positioned 50 cm in front of the participant. The instructions were visually presented on the screen. Participants were instructed to locate a target stimulus as quickly as possible and indicate its orientation by pressing one out of two identical orientations on a button box, developed for experimental testing (see figure 1).

6

In the center of the screen, a short instruction was presented before each trial during 1250 ms. Each block consisted of 24 trials, including 12 trials with a new configuration and 12 trials with a configuration that was repeated throughout the experiment (once in every block). Target position in both repeated and new trials were randomly defined from the same set of positions. Only the positions of the items in the repeated configuration were constant. The participant had to press a button to start the practice phase. During practice, 24 trials were given, including only new spatial configurations. If participant did not understand the task after the practice session, or was still making many errors, the practice trials were repeated until a full understanding of the procedure was established. After practice the experiment started with instructions on the computer screen. 16 Blocks were presented on the screen. After each block a 10 second interval was given to assure a short rest after each block. Moreover, instructions were repeated after the interval to assure the goal of the task to be known. Subjects could manually continue the experiment by pressing the button with the left orientation.

Table 2. Demographic variables, neuropsychological test results, and radiological finding of the Korsakoff's patients

Patient	Gender	Age	Handedness[a]	Education[b]	IQ[c]	Verbal learning[d]	RBMT[e]	Spatial Span[f]	Radiological findings [g]
1	M	62	Right	3	94	<1	8	5	Diffuse WML and mild degeneration MB*
2	F	47	Right	4	95	1-5	7	5	Mild WML*
3	F	44	Right	5	92	<1	7	5	Mild degeneration MB*
4	M	48	Right	5	101	<1	4	5	Mild diffuse cortical atrophy*
5	M	46	Bidextral	5	103	5-15	17	4	Cortical atrophy; degeneration diencephalon including MB*
6	F	42	Left	4	81	<1	8	5	Mild cortical and cerebellar atrophy, degeneration of MB*
7	M	47	Left	6	107	5-15	8	7	Degeneration of MB*
8	M	57	Right	6	115	1-5	8	7	No abnormalities*
9	M	53	Right	4	105	<1	5	6	Cortical atrophy and mild degeneration of MB*
10	M	61	Right	4	104	<1	2	6	Cortical and cerebellar atrophy**
11	F	61	Right	3	94	<1	3	5	Mild frontal WML; mild degeneration of MB*
12	M	57	Right	5	97	<1	1	5	Diffuse cortical atrophy**
13	M	59	Right	4	87	<1	12	4	No abnormalities**
14	F	50	Right	4	88	<1	4	N.A.	No abnormalities**
15	M	62	Right	4	97	<1	6	5	WML; degeneration of MB*
16	F	51	Left	5	109	<1	4	5	Mild cerebellar atrophy, mild degeneration of MB*
17	M	49	Right	4	102	5-15	2	5	N.A.
18	M	64	Right	5	95	5-15	2	N.A.	Mild cortical atrophy*
		M =53.3 SD = 7.1		M = 4.4 SD = 0.9	M = 98.1 SD = 8.5				

N.A. = not available, Education = Education level, TOL = Tower of London, RBMT = Rivermead Behavioural Memory Test, c.m. = Corpuscle Mammilary

[a] Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971)
[b] Education level, was scored using 7 categories: 1 = lowest (less than primary school), 7 = highest (university degree) (Verhage, 1964).
[c] IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).
[d] Percentile scores for the total performance on the first five learning trials, measured with the Dutch version of the California Verbal Learning Test, for measurement of long-term memory (Mulder et al., 1996).
[e] Raw scores. Memory test for everyday memory. <10 = serious disturbance, 10-15 = moderate disturbance, 16-21 = light disturbance (Van Balen & Wimmers, 1992).
[f] Corsi Block-Tapping Test forward span, reflecting attention and spatial working memory (Kessels et al., 2000).
[g] Tower of London is presumed to asses central executive functioning, in particular planning and problem solving (Kafer & Hunter, 1997). In a reference group the mean score is 30.6, SD = 2.7 (Ganzevles et al., 1994). h Neuroradiological examination by magnetic resonance imaging (MRI) scan* or CT scan **.

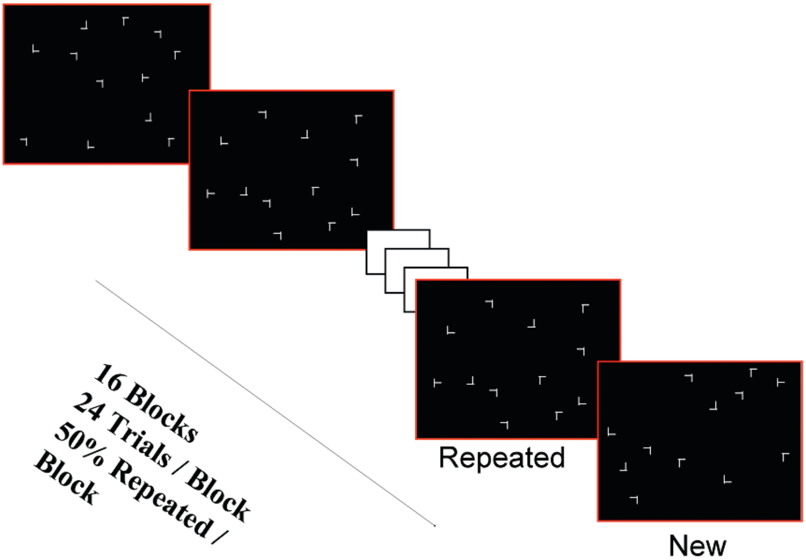


Figure 1. Example of a display in the implicit contextual learning task. 50% of the configurations were repeated throughout the experiment and 50% were randomly generated.

Immediately after finishing the task, an awareness check was performed by asking all participants the following three questions: (1) 'Did you notice anything during the experiment?' (2) 'Did you notice that some of the configurations were repeated?' (3) 'Did you try to remember the repeated configurations?' Finally, in order to verify whether context information was memorized implicitly, a Recognition memory control task was applied. This task consisted of 24 trials, including the 12 configurations that were repeated during the contextual cueing task and 12 new configurations. Repeated and new configurations were presented in a random order and participants were instructed to indicate whether the configuration was repeated during the experiment by pressing "yes" or "no" on the button box.

Procedure for the Box task

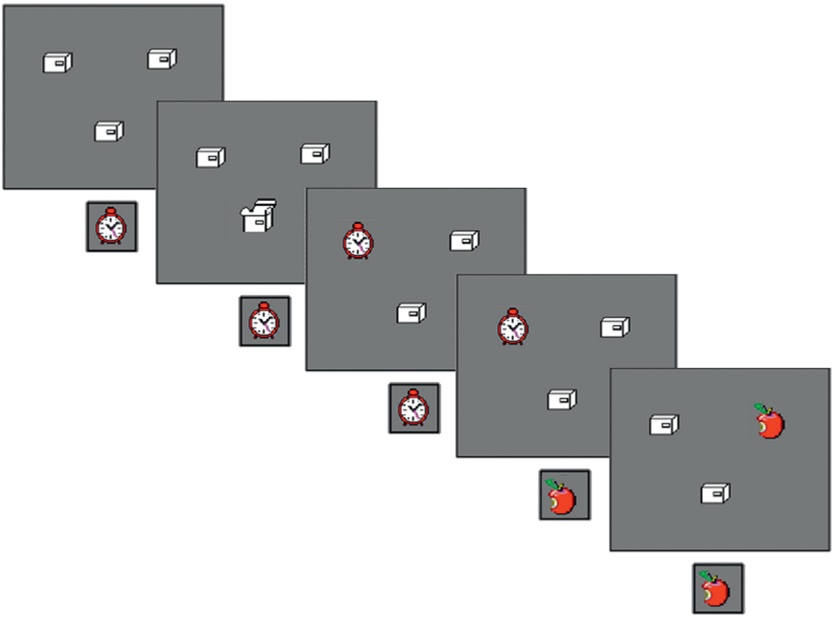


Figure 2. Example of a search display in the Box task for a search through three boxes. Two target objects (clock, apple) are presented. In the fourth picture, an error trial is illustrated.

For the Box task, pictures of closed boxes were displayed on different locations within a square of 28.5° × 29.7° on a 15" touch-sensitive LCD computer monitor (ELO AccuTouch, 2001). Each trial (see figure 2), a colored target object (e.g. apple, clock) was presented in icon-format (±1.6° by 1.6°). Participants were instructed to find the target object, which was hidden in one of the white boxes (± 1.6° by 1.6° cm). By touching them, the boxes could be opened, after which an empty box or the target object was shown. Empty boxes remained open for two seconds, while the target was shown until the participant initiated a new search for a new target object. This new object was shown after the participants pressed a 'Start' button on the screen. Importantly, a target object that was found remained in the box and was the only object that could be located in that box. In the search for a new target object participants had to remember which object was previously filled with an object, because this object remained in this box. After locating objects in all boxes shown on the screen a new set of boxes was presented. The task began with two practice trials of three boxes, after which two trials of four, six, eight and ten boxes were used (see Van Asselen et al, 2005, and Kessels et al., 2010, for a more detailed description of the task). No time limit was set.

Analysis for the Implicit Contextual Learning Task

The total implicit contextual learning task consisted of 16 blocks. Before analysis, all response times longer than 20 seconds were removed as outliers. Furthermore, trials in which an error was made were excluded from the analyses on implicit contextual learning as well as trials with a response time longer than 2 SD above the individual mean (Barnett & Lewis, 1994). For statistical analysis, the blocks were collapsed into 4 epochs of 4 blocks each. In line with previous patient studies and the original report of implicit contextual learning, we only used the second half of the experiment for statistical analysis (Chun & Jiang, 1998; Chun & Phelps, 1999; Manns & Squire, 2001; Van Asselen et al., 2009). For the implicit contextual learning task a 2 × 2 × 2 repeated measures ANOVA with 'epoch' (epoch 3 and 4) and 'type' (repeated and novel configurations) as within-factors and 'group' (patients and control participants) as between-factor was performed. The main variable of interest was the interaction between the contextual learning effect (factor 'type') and both groups (patients and controls). To quantify the results of the statistical analysis, contextual learning was measured as the difference in reaction times between repeated and novel items.

Analysis for the Box task

Set size is defined as the total number of boxes. For a set size of 4, 4 objects need to be located in separate boxes. One search is defined as the boxes that a participant needs to open to locate one object in the presented boxes. A trial is defined as all searches for one set size.

Three types of measures were defined (Van Asselen et al, 2005):

1) Within-search errors were made when a participant returned to an already opened box within one search. The number of within-search errors was calculated by accumulating the total number of within-search errors per set size.

2) Between-search errors were made when a participant returned to a box where a target object was found in one of the previous searches. The total number of between-search errors was calculated by accumulating the total number of between-search errors per set size.

Both measures were analyzed separately by means of a 2 × 4 repeated measures ANOVA including the between-subject factor 'group' (patients and control participants) and the within-subject factor 'set size' (4,6,8,10 boxes). Three 2 × 2 repeated measures ANOVA were performed to calculate differences for the transitions between the within-subjects factor 'set size' (4 and 6; 6 and 8; 8 and 10) and the between-subject factor 'group' (patients and control participants).

Correlational analysis

Pearson's correlation coefficients (*r*, two-tailed) were calculated for the average search times on novel items in the implicit contextual learning task and the total numbers of between-errors and within-errors in the Box task to investigate the relationship between spatial working memory and contextual learning. Pearson's *r* was also computed for the contextual learning effect, calculated as the total difference between the reaction times on repeated and novel items in the implicit contextual learning task, and the between-errors and within-errors in the Box task to elucidate a possible relationship between search efficiency and spatial working memory.

Results

Implicit Contextual Learning task

Figure 3 depicts the average reaction times per epoch for new and repeated items in the implicit contextual learning task in patients and controls. Although both KS patients and controls made a small number of errors, patients made significantly more errors than controls [patients: 3.2 % (SD=2.7%), controls: 0.6% (SD=0.6%), $t(38) = 4.2$, $p<0.001$]. Furthermore, few trials were excluded because of delayed response [patients: 4.0% (SD=0.9%), controls: 4.0% (SD=0.7%)].

A significant main effect for stimulus type was found [$F(1,38) = 18.7$, $p<0.001$], indicating that reaction times were faster on repeated items compared to new items. Furthermore, an effect of epoch was determined [$F(1,38) = 9.4$, $p<0.01$], indicating that reaction times in the last epoch were faster than reaction times in the third epoch. Moreover, a group effect [$F(1,38) =13.5$, $p<0.001$] was found, indicating that overall patients were slower than controls. Importantly, the group × type interaction was not significant [$F(1,38) = 0.17$, $p=0.69$], which shows that implicit contextual learning in the KS patient group was not different from implicit contextual learning in the control group. For patients an average contextual learning of 137.1 ms was found (SD=253.6), while for control subjects this was 165.7 ms **(SD=188.9).**

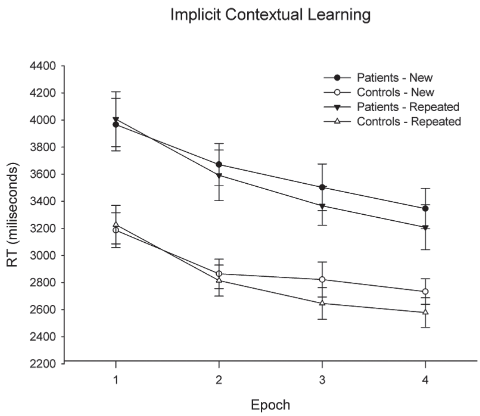


Figure 3. Mean reaction times (RT) in milliseconds (ms) for the Repeated and New trials as a function of Epoch (1–4) for Korsakoff's syndrome patients (n=18) and the control group (n=22). Error bars indicate standard error of the mean.

Furthermore, the type × epoch interaction was not significant [F(1,38) =0.02, p=0.88], indicating that for epoch 3 the difference in response times between repeated and new were identical for epoch 4. Also, the type × epoch × group interaction was not significant [F(1,38) =0.03, p=0.86], showing that both patients and controls showed no relative difference in reaction times on epoch 3 and 4 for repeated and novel items.

In light of the slower visual search in the KS patient group relative to the control group, we determined whether differences in the magnitude of learning was apparent on a measure that equated speed by expressing learning as a proportion of one's baseline speed (i.e., novel – repeated/novel, calculated per epoch; see Barnes et al., 2008 for a more detailed description of the procedure). Proportional learning scores computed for each participant were analyzed in a group × epoch ANOVA. The main effect of group [F(1,38) =0.84, p=0.37] and the group × epoch interaction [F(1,38) =0.146, p=0.71] were not significant, indicating that measures of proportional learning did not differ between the KS patient group and the control group. For patients an average proportional contextual learning of 3.8% (SD=7.1%) was found, while for control subjects this was 5.7% (SD=6.5%).

Recognition Memory

None of the participants spontaneously reported to have noticed the repeated configurations spontaneously, and no participant reported this after being explicitly asked. Importantly, explicit recognition of repeated configurations was not above chance level for both the patient and control group (patients: 50.2% (SD=8.9) pooled hits and correct rejections, [$t(17) = 0.1$, $p=0.91$)], controls: 51.4% (SD=9.9) pooled hits and correct rejections [$t(21) = 0.7$, $p=0.52$]). This indicates that the observed learning effect is not the result of explicit knowledge of the location of the target. Moreover, the percentage of hits during the recognition task was not significantly different between both groups [patients: 47.2% (SD=27.8%), controls 42.7% (SD=28.7%), $t(38) = 0.5$, $p=0.62$], neither was the number of false alarms [patients: 46.8% (SD=23.9%), controls 40.8% (SD=27.9%), $t(42) = 0.7$, $p=0.48$], indicating that both patients and controls do not show explicit recognition to the same extent.

Results for the Box task - Within-search errors

Relatively few within-search errors were made by the patient and control group in absolute terms (see figure 4). Patients did not make more within errors than controls [$F(1,38) = 2.5$, $p=0.13$]. A main effect was found for set size [$F(3,114) = 16.3$, $p<0.001$]. Post-hoc testing indicate that more errors were made in the condition with ten boxes than eight boxes [$F(1,38) = 5.9$, $p<0.05$], eight than six boxes [$F(1,38) = 23.1$, $p<0.001$], but not six than four boxes [$F(1,38) = 2.6$, $p=0.11$]. However, the group × set size interaction was not significant [$F(3,114) = 1.9$, $p=0.12$] indicating that both groups performed identical for all set sizes.

Between-search errors

KS patients made more between-search errors than control participants [$F(1,38) = 38.2$, $p<0.001$]. A main effect was found for set size $F(3,114) = 123.4$, $p<0.001$]. Post-hoc tests (see figure 4) indicated that more errors were made in the condition with ten boxes than eight boxes [$F(1,38) = 32.1$, $p<0.001$], eight than six boxes [$F(1,38) = 129.4$, $p<0.001$], and six than four boxes $F(1, 38) = 47.2$, $p<0.001$]. The group × set size interaction was significant [$F(3,114) = 7,9$ $p<0.001$]. Post-hoc tests indicate that KS patients were more impaired than controls for the transition from four to six boxes [$F(1,38) = 20.2$, $p<0.001$] and six to eight boxes [$F(1,38) = 11.5$, $p<0.005$], but not for eight to ten boxes [$F(1,38) = 0.4$, $p=0.54$].

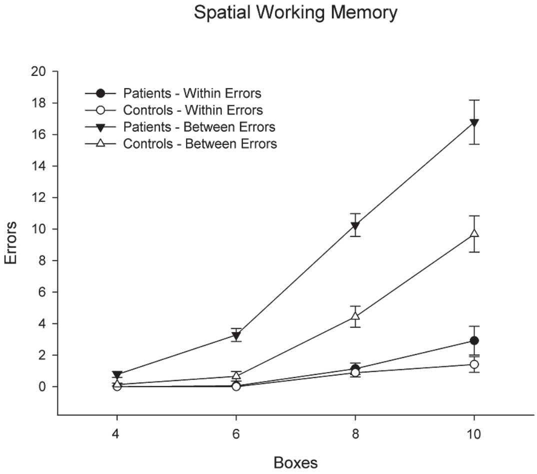


Figure 4. Average number of Within- and Between-search errors (Set sizes 4, 6, 8, 10) for Korsakoff's syndrome patients (n=22) and the control participants (n=18). Error bars indicate standard error of the mean.

Correlational analysis

The average search times on new, unrepeated items of the implicit contextual learning paradigm was positively correlated with the total number of between-search errors [r(39) = 0.47, p<0.005], indicating that there is a moderate relationship between speed of processing in the implicit contextual learning task and number of errors on explicit spatial working memory in the Box task. However, the implicit contextual learning effect showed no relation with between-search errors [r(39) =-0.07, p =0.67], suggesting that implicit contextual learning is dissociable from explicit spatial working memory as measured by the Box task. The average search times on new items of the implicit contextual earning paradigm did not significantly correlate with the total number of within-search errors [r(39) = 0.10, p=0.55], neither did implicit contextual learning [r(39) = -0.22, p=0.18]. This suggests that short-span spatial working memory is not related to search efficiency or implicit contextual learning.

Discussion

The aim of this study was to investigate whether patients with Korsakoff's syndrome (KS) are able to implicitly learn spatial regularities despite marked problems with regard to conscious memory operations. In order to further examine the interrelations between implicit and explicit spatial memory influences we directly compared performance on an implicit spatial memory task to spatial working memory scores in KS. The results of the present study indicate that individuals with Korsakoff's syndrome (KS) show intact ability to acquire contextual information from our environment after repeated presentation without conscious awareness. This is in contrast with the severely impaired spatial working memory performance in KS as measured by the between-search errors in the Box task. This underscores that implicit spatial learning and conscious spatial memory have a different neurocognitive basis. In line with this we observed no correlation between the Box task performance and the Implicit context learning. Interestingly, average search times on new items in the implicit contextual learning paradigm showed a negative correlation with performance on the Box task. This suggest that general search efficiency is related to working memory, whereas implicit contextual learning is not.

The results of this study are in line with previous observations of intact unconscious influence on spatial memory in KS (Postma et al., 2008) and support several other studies on verbal and procedural implicit memory in KS reporting intact implicit memory (Graf et al., 1985; Cermak et al., 1991; Verfaellie et al., 1996, Fama et al., 2006, d'Ydewalle & Van Damme, 2007, Van Damme & d'Ydewalle, 2009). Conversely, an important difference between previous studies on implicit learning and the current study is the fact that implicit contextual learning is not based on the association between perception and motor responses, or verbal material, but is a pure and direct measure of implicit spatial memory (Chun et al., 2000; Van Asselen et al., 2009). The results of this study contradict evidence for diminished implicit memory in KS (e.g. Verfaellie et al., 1992; Brunfaut & d'Ydewalle, 1996) or suggestions that implicit memory in KS is merely the result of enhanced instructions (Swinnen et al., 2004) or findings of relatively diminished implicit spatial memory in KS (Verfaellie et al., 1992; Van Tilborg et al., 2011). Moreover, the results of our study indicate that not all individuals with amnesia experience impaired implicit spatial learning. Previous research on amnesic patients with medial temporal lobe amnesia showed no implicit spatial memory after rehearsal (Chun & Phelps, 1999). Manns and Squire (2001) suggested that more extensive damage to the temporal lobe is crucial to find diminished implicit spatial learning.

One of the strengths of the current study compared to earlier studies on implicit memory in KS is the relatively large sample size of KS patients (n=18) that have been recruited for this study. While recent studies indicative of intact implicit memory in KS recruited groups with comparable size (d'Ydewalle & Van Damme, 2007; Postma et al., 2008; Van Damme & d'Ydewalle, 2009), earlier evidence was sometimes based on very small groups with limited power. Since most reports on disturbed implicit memory in KS have sample sizes smaller than ten patients (Verfaellie et al., 1992; Brunfaut & d'Ydewalle, 1996; Swinnen et al., 2004), these studies are more vulnerable to random sample variations affecting the conclusions of the studies. However, divergent observations on implicit memory performance in amnestics in the literature possibly also indicates that the presence or absence of difference with healthy volunteers depends on the type of task that is used and the subform of implicit memory that is being studied (Ostergaard, 1999; Postma et al., 2008, Van Tilborg et al., 2011). Moreover, previous studies applied various types of implicit contextual learning paradigms that varied greatly with respect to number and type of trials. Systematic and direct comparison of different implicit learning paradigms may shed light onto some of the discrepancies.. Therefore, this question warrants investigation in future studies.

The results on the Box task replicate and extend earlier results reported for KS patients (Van Asselen et al., 2005). The profile for within-search errors followed a comparable pattern in the current research and the original report. However, the number of within-search errors did not differ between the KS patients and controls, while in the original study by van Asselen and colleagues (2005) a significant difference was obtained also for the within-search errors, albeit that absolute differences and effect sizes were small. This discrepancy possibly relates to subtle differences between both studies; such as higher educational levels for the current patient group and somewhat more stringent inclusion criteria for the current study (e.g. IQ > 80, to exclude possible cases of alcohol dementia). Although it could be expected to find more within-search errors for higher working memory loads in the KS patient group compared to controls, no such relationship became clear. Nevertheless, between-search errors, indicative of elaborated processing in spatial working memory, become progressively more prominent in KS with higher working memory loads. Importantly, in order to avoid between-search errors in the box task, spatial information has to be kept in memory over a longer time period, whereas the Corsi Block Tapping task requires spatial information to be kept in memory over a very short time period (Van Asselen et al., 2006). This possibly explains why all patients had intact visuospatial short-term memory span (Table 2) while more between-search errors became evident in the box task. The pattern of errors of the current study indicate that spatial working memory is hampered in KS, but specifically the transition of information from short span to middle long span is affected, reflected by the significant problems during between-search.

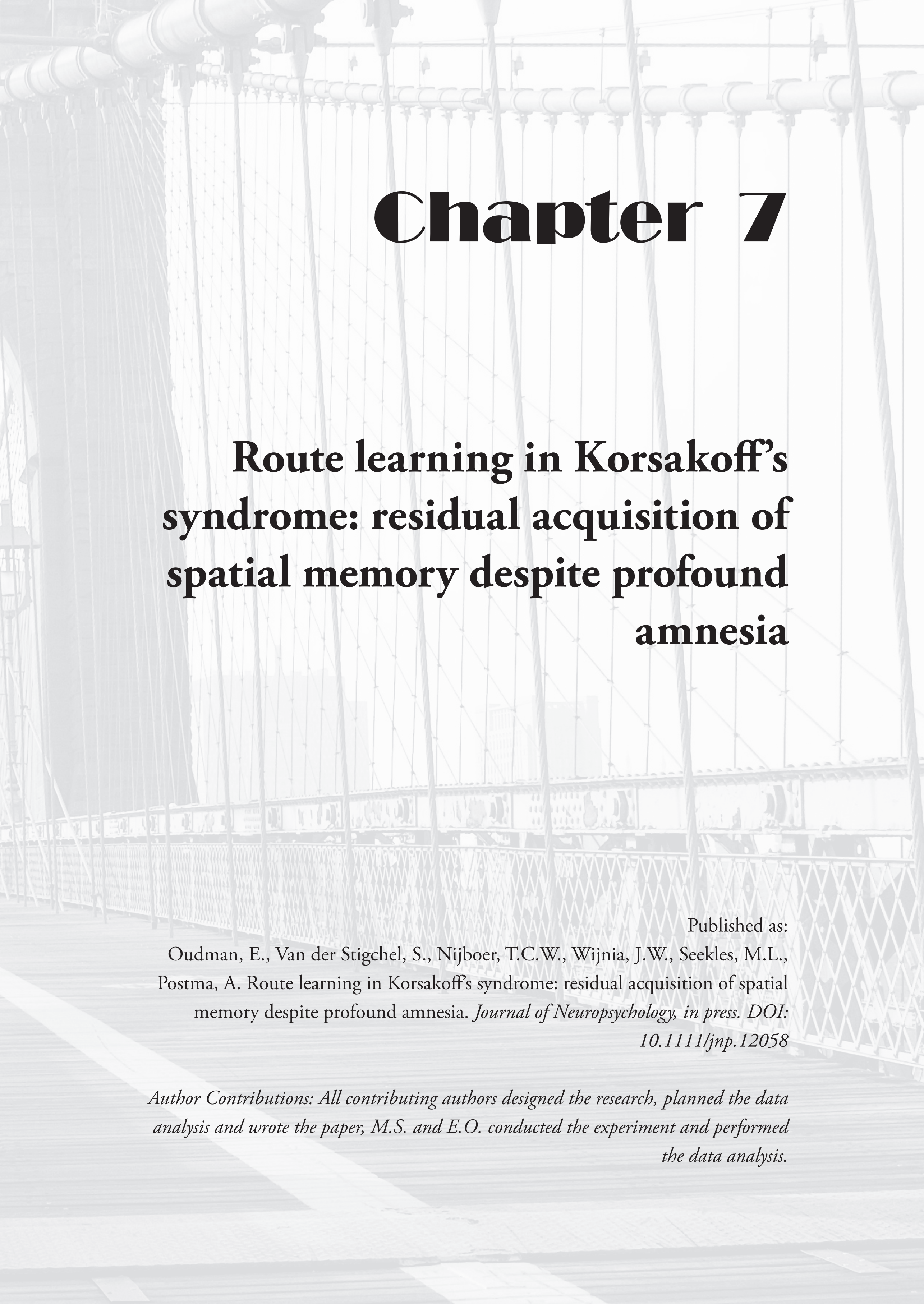
Previous research has indicated that specifically damage to both the right dorsolateral prefrontal cortex and right posterior parietal cortex was correlated with the number of between-search errors in stroke patients during a comparable Box task as applied in our study (Van Asselen et al., 2006). The results of the current study appear to be in line with this finding, since KS is known to damage the prefrontal cortices (e.g. Kopelman, 2009). However, we should be cautious with respect to relating our findings to the specific lesion locations, since the lesions in Korsakoff patients are not limited to the prefrontal cortex or the diencephalon (see also Table 2).

Recent evidence shows that the basal ganglia are of critical importance for implicit contextual learning, since both patients with Parkinson's disease or Huntington's disease show no evidence for intact implicit contextual learning (Van Asselen et al. 2009, 2010). Although the aim of the current study was not to unravel the underlying neural structures in detail, previous neuroimaging studies found evidence for damage to the dorsomedial thalamus and mammilary bodies in KS patients. The results of our study therefore stress the importance of differentiating between subcortical structures underlying memory functions, since KS is profoundly known for its diencephalic disturbance, but not the basal ganglia (Kopelman, 1995; Sullivan & Pfefferbaum, 2009).

Conclusion

In conclusion, this study has demonstrated that individuals with Korsakoff's syndrome (KS) show intact ability to acquire contextual information from the environment after repeated presentation without conscious awareness. They do so to the same degree as matched healthy controls. This implicit contextual learning was found to be unrelated to spatial working memory performance, whereas general search times on new items were related to implicit contextual learning. This suggests that intact implicit contextual learning in KS is not directly related to spatial working memory.

Together these results suggest that implicit and explicit spatial memory have a different neurocognitive basis. Moreover, this study suggests that a clear distinction can be made between damaged implicit contextual learning in Parkinson's and Huntington's disease after subcortical damage to the basal ganglia, compared to subcortical damage in KS.



Chapter 7

Route learning in Korsakoff's syndrome: residual acquisition of spatial memory despite profound amnesia

Published as:
Oudman, E., Van der Stigchel, S., Nijboer, T.C.W., Wijnia, J.W., Seekles, M.L., Postma, A. Route learning in Korsakoff's syndrome: residual acquisition of spatial memory despite profound amnesia. *Journal of Neuropsychology, in press. DOI: 10.1111/jnp.12058*

Author Contributions: All contributing authors designed the research, planned the data analysis and wrote the paper, M.S. and E.O. conducted the experiment and performed the data analysis.

Abstract

Korsakoff's syndrome (KS) is characterized by explicit amnesia, but relatively spared implicit memory. The aim of this study was to assess to what extent KS patients can acquire spatial information while performing a spatial navigation task. Furthermore, we examined whether residual spatial acquisition in KS was based on automatic or effortful coding processes. Therefore, twenty KS patients and twenty matched healthy controls performed six tasks on spatial navigation after they navigated through a residential area. Ten participants per group were instructed to pay close attention (intentional condition), while ten received mock instructions (incidental condition). KS patients showed hampered performance on a majority of tasks, yet their performance was superior to chance level on a route time and distance estimation tasks, a map drawing task and a route walking task. Performance was relatively spared on the route distance estimation task, but there were large variations between participants. Acquisition in KS was automatic rather than effortful, since no significant differences were obtained between the intentional and incidental condition on any task, whereas for the healthy controls the intention to learn was beneficial for the map drawing task and the route walking task. The results of the current study suggest that KS patients are still able to acquire spatial information during navigation on multiple domains despite the presence of the explicit amnesia. Residual acquisition is most likely based on automatic coding processes.

Introduction

Korsakoff's syndrome (KS) is a chronic neuropsychiatric disorder caused by thiamine deficiency typically following prolonged excessive alcohol abuse and self-neglect. KS is characterized by severe anterograde amnesia affecting all domains of explicit memory (Kopelman, 1995). There is, however, evidence that KS patients have even more pronounced problems in remembering contextual information, such as spatial memory for coordinate (exact locations of objects in space) as well as categorical (relative) object to location binding (Kessels, Postma, Wester, & de Haan, 2000). Also, forming associations between temporal order information and spatial information is severely hampered (Postma, Van Asselen, Keuper, Wester, & Kessels, 2006). Although the syndrome is characterized by severe impairments in learning and remembering contextual information explicitly, implicit learning of contextual information seems relatively preserved in KS (Hayes, Fortier, Levine, Milberg, & McGlinchey, 2012). It has, for example, been shown that patients with KS show intact ability to acquire contextual information after repeated presentation, resulting in faster localization of a target in the environment (Oudman, Van der Stigchel, Wester, Kessels, & Postma, 2011). Moreover, Postma, Antonides, Wester, and Kessels (2008) illustrated that KS patients demonstrated unconscious influence of spatial configurations on a subsequent task in an object-location memory paradigm. Both studies indicate that despite the severity of cognitive deterioration in KS, patients are still able to retrieve some contextual information implicitly.

A daily activity which requires processing of temporal and spatial information is spatial navigation. Although several studies have been performed on learning of computerized spatial tasks in KS patients, surprisingly little research has been performed on actual spatial navigation (see Kessels & Kopelman, 2012 for a review). Spatial navigation concerns remembering where things are and applying this information to get from one location to another, for example while walking or driving from one place to another (Postma, van Oers, Back, & Plukaard, 2012). Automatic processing of spatial information would be advantageous in such complex daily activities. Hasher and Zacks (1979) made the distinction between automatic and effortful processing of spatial information. The authors argued that because of its ecological significance spatial memory operates mainly or even fully automatically, that is, without direct attention and intent. Several studies have supported that at least some information is automatically encoded during spatial navigation. For example, when not paying any attention to a new environment, we will most likely still be able to remember, or at least recognize some familiar landmarks and remember the temporal position of the landmarks along the route (Cornell, Heth, & Alberts, 1994). Moreover, a global sense of direction does not necessary require effort (Postma et al., 2008). Others, however, have found better performance on spatial navigation when locations were encoded intentionally (Light & Zelinski 1983). Recent studies on spatial navigation emphasized different aspects of route learning in the light of automaticity. Van Asselen, Fritschy, and Postma (2006) showed that without the instruction to remember a route, participants performed equally compared to those who were instructed to remember the route on tasks involving landmark information and route knowledge, such as landmark recognition and landmark ordering. Survey knowledge, such as drawing a map-like presentation and walking the route in reverse was hampered. The results of this study suggest that some aspects of spatial navigation are automatically coded, but some others are not.

Not only has the topic of route learning and navigation rarely been investigated in KS, the issue of automatic acquisition is still largely unexplored. This is remarkable because automatic navigation is relevant in everyday life for both healthy persons as patients with KS. The finding that some aspects of spatial navigation are processed automatically is of interest since this could suggest that despite the presence of amnesia in KS residual acquisition of information relevant to spatial navigation might still be available. To our knowledge, however, this has never been the topic of investigation. To date, there has been only one study on repeated route walking in KS (Kessels, van Loon, & Wester, 2007). The primary goal of this study was to evaluate the effectiveness of the errorless learning teaching technique in KS, showing no beneficial effect compared to trial-and-error learning with respect to taking the correct turns on the route. The study did not involve a healthy control group. Moreover, a recent study suggested that errorless learning could in fact be beneficial for skill learning in KS, dependent on the task at hand (Oudman, Nijboer, Wijnia, Kerklaan, Lindsen, & Van der Stigchel, 2013).

In light of the foregoing, the main objective of the current study was to examine whether KS patients still have some potential for acquisition of specific spatial information during spatial navigation. The present study therefore adopted six tasks targeting typical aspects of spatial navigation that have previously been applied in studies in healthy subjects (Van Asselen et al., 2006) and stroke patients (van der

Ham, van Zandvoort, Meilinger, Bosch, Kant, & Postma, 2010). The tasks intended to assess time and distance estimation, landmark recognition and ordering, map drawing and actual route memory in KS patients and healthy controls after they have navigated through a residential area. In order to further examine whether KS patients had some potential to acquire spatial information during spatial navigation chance performance was calculated for all six tests by asking a group of healthy controls to perform the tasks without having experienced the original route. Additionally, we also wanted to elucidate whether any residual acquisition in KS was explained by either automatic or effortful processes. Since KS is characterized by severe impairments in effortful contextual memory (Kessels et al., 2000), it could be expected that acquisition of spatial information in KS is based on automatic processes. Therefore, the participants were included in an incidental (automatic processes) or intentional condition (automatic and effortful processes). When effortful processes are required for acquisition during spatial navigation, performance would improve under intentional learning conditions. In contrast, if automatic processes would suffice, no difference between the two conditions would be found. Based on the severity of the amnesia in KS we expected residual acquisition in KS to be based on automatic, rather than effortful processes.

Methods

Participants

Twenty-three patients with severe anterograde amnesia, diagnosed with KS participated in this study. The patients were inpatients of a Korsakoff Center in The Netherlands. All patients fulfilled the DSM-IV criteria for alcohol-induced persisting amnestic disorder (APA, 2000) and the criteria for KS described by Kopelman (2002). The amnestic syndrome was confirmed by neuropsychological testing. All patients were in the chronic, amnestic stage of the syndrome, and none were in the confusional Wernicke psychosis at time of testing. Premorbid IQ was estimated with the Dutch Adult Reading Test (Schmand, Lindeboom, & Van Harskamp, 1992), which is the Dutch version of the National Adult Reading Test (Christensen, Hazdi-Pavlovic, & Jacomb, 1991). All included patients had an estimated IQ score above 80, to exclude patients with low intellectual or cognitive functioning interfering with the testing procedure, possibly caused by alcohol dementia (Oslin, Atkinson, Smith, & Hendrie, 1998). All patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts. Selected patients did not show neurological disorders (head injury, epilepsy, etc.) or acute psychiatric conditions (psychosis, major depression, etc.) interfering with the testing procedure. All patients were administered a Dutch version of the Rey Verbal Learning Test (Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005), a task measuring verbal immediate and long-term memory and scored within the first to the fifth percentile on the total number of words recalled in Trials 1-5. Table 2 shows a summary of demographic variables and neuropsychological test results for all patients. Additionally, twenty age- and premorbid IQ matched controls were included and performed the exact same tasks as the patients with KS. Last, fifteen healthy participants were included in a control experiment (see below). The study was conducted in accordance to the standards of the declaration of Helsinki. All participants gave informed consent prior to their inclusion in the study.

General Procedure

The twenty-three patients and twenty control participants were randomly assigned to the intentional and incidental group. Participants in the intentional group were told that the aim of the experiment was to study route-learning behavior during a fresh walk outside. They were asked to pay attention to the route they were going to walk, since they would be tested on their knowledge of this route. Participants in the incidental group were told that they needed to accompany the experimenter during a walk outside, to test the effects of fresh air on attention. Both groups walked the same route outside the Korsakoff Center in a neighboring residential area. At the end of the experiment, participants were asked to indicate whether they had been in the specific residential area before. None of the participants indicated that they had been in this specific residential area before. The route was 400 meters. In both groups, conversation was limited to responding shortly but politely to any questions that were asked or comments that were made by the participants. To secure that the walking speed was comparable for all participants the experimenter explicitly tried to maintain a standard walking gait. This standard walking gait was practiced by the experimenter before the experiment. Since we did not want to give any cue to the participants in the incidental condition about the true aim of the study, we chose not to measure time or walking speed. When participants arrived in the test room, they were engaged in distraction tasks for about 25 min. These tasks involved the Location Learning Test (Bucks & Willison, 1997; Kessels et al., 2006), the Corsi Block Tapping Test (Kessels, Van Den Berg, Ruis, & Brands, 2008) and the Dutch Adult Reading Test (Schmand et al., 1992). The tests were intended to avoid active rehearsal of the spatial information by the participants (see Table 1 for test results). Next, participants in the incidental group were informed about the true aim of the study. Subsequently, all participants performed six tasks that tested selective aspects of their spatial knowledge. After the final task was performed (Route Walking Task) participants were asked whether they were familiar with the route. None of the patients or control participants mentioned familiarity with the residential area. In the control experiment, healthy participants in the chance condition were instructed to perform the aforementioned six tasks that tested selective aspects of their spatial knowledge by guessing i.e. without having seen the original route.

Tasks

Six tasks were included in the current experiment:

1. Landmark Recognition Task: Sixteen photographs were presented, all of them including a landmark that characterizes either a path (e.g., a red garbage can) or a decision point (e.g., a bicycle rack). Nine photographs were taken along the route (targets) and seven photos were taken in the same area, but not along the route (distractors). Participants had to indicate whether they recognized the landmarks from the route or not and they had to guess if they did not know the answer. The target landmarks are represented in Figure 1. The proportion of correct responses was calculated (Range: 0-100%).

2. Landmark Ordering Task: Participants were shown six photographs of landmarks taken along the route and were asked to place the photos in the right order, from first seen landmark to last seen landmark. If the participants did not know the right order, they had to guess. Participants received two points for a picture on its correct location, one for a picture in a position adjacent to its correct position and zero points for all others (Range: 0-12 points).

3. Map Drawing Task: Participants were shown a map of the area in which they had walked a route and were given the instruction to draw the route on the map (see Figure 1). The starting point was given by the researcher. One point was given for each correct decision point that

was included and another one when the right direction was chosen at a decision point. Moreover, one point was subtracted for each passed decision point that was not along the route. (Range: 0-29 points).

4. Time Estimation Task: Participants were asked to estimate the time it took to walk the route (circa six minutes). The correct answer was subtracted from the estimated answer to calculate the size of the error. There were no minimum or maximum scores on this task.

5. Route Length Estimation Task: Participants were asked to estimate the distance of the route (400 meters). The correct answer was subtracted from the estimated answer in order to calculate the size of the error. There were no minimum or maximum scores on this task.

6. Route Walking Task: Participants had to navigate the route from beginning to the end. The researcher walked along with the participants and corrected them if they made a wrong turn. The number of correct turns was counted (Range: 0-15 correct turns).

Figure 1. A map of the residential area showing the route that participants walked during the learning phase, and the positions of landmarks along the route.

Analysis

In line with a previous report on route acquisition (Van Asselen et al., 2006) a MANOVA was used with a within-subject variable Task (landmark recognition, landmark ordering, route time estimation, route distance estimation, map drawing task, route walking task) and the between-subject variables Group (patient and controls) and Condition (intentional and incidental). Both results of the MANOVA and subsequent ANOVAs are presented. In the control experiment, the performance of KS patients per subtest was compared to performance of the healthy control chance group by means ANOVAs (chance group and KS patients). A p-value of less than .05 was considered statistically significant.

Results

Demographic variables and neuropsychological results

Three patients were excluded from analysis because they were unable to complete the experiment without physical assistance of a transport wheelchair pushed by a member of the nursing staff. The remaining twenty patients and twenty healthy controls were included in the analysis. In the control experiment, fifteen additional healthy participants were enrolled. They were mainly adult visitors of an open day of the institute and were about evenly divided between men and woman. Table 1 gives a summary of demographic variables and neuropsychological test results for the patient groups and the healthy control groups, split on condition (intentional versus incidental).

Table 1. Demographic variables and neuropsychological test results for the Korsakoff's patients (n=20) and healthy controls (n=20) for the incidental and intentional condition (n=10 per condition). A GLM univariate analysis was used for the individual subtests with the between-subject variable Group (Korsakoff's syndrome patients and Controls) and Condition (intentional and incidental condition).

	Korsakoff's patients		Healthy Controls				
	Intentional Condition	Incidental Condition	Intentional Condition	Incidental Condition	Group-effect F-Value	Condition-efect F-Value	Group X Condition-effect F-Value
Number of participants (m, f)	10 (7:3)	10 (8:2)	10 (3:7)	10 (5:5)			
Age (*M*, *SD*)	59.6 (9.2)	59.4 (6.3)	58.3 (8.6)	52.7 (9.3)	2.2	1.1	1.0
IQ (*M*, *SD*)[a]	97 (12.3)	101 (13.4)	101.4 (12.1)	100.7 (7.0)	0.3	0.2	0.4
Corsi Span Forward (*M*, *SD*) [b]	5 (0.5)	5.1 (0.9)	5.5 (0.9)	4.9 (0.9)	0.4	1.0	1.9
Corsi Span Backward (*M*, *SD*) [b]	4.7 (1.2)	5.3 (0.8)	5.6 (0.7)	5.3 (0.9)	2.4	0.3	2.4
Location Learning Test - Learning Index (*M*, *SD*) [c]	14.9 (9.4)	24 (17.7)	64.9 (30.1)	46.8 (31.8)	22.8*	0.3	3.2

Note. m, male; f, female; *M*, mean; *SD*, standard deviation; * p < .001 .[a] IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).[b] Corsi Block-Tapping Test, reflecting visuospatial memory (Kessels et al., 2008). [c] Learning error (displacement score) was calculated for the Location Learning Test (Bucks, & Willison, 2004; Kessels, et al., 2006). Learning error in the reference group was M=8.1, SD=6.6.

Table 2 shows a summary of demographic variables and neuropsychological test results for all patients.

Table 2. Demographic variables and neuropsychological test results of the Korsakoff's patients (n=20).

Patient	Gender	Age	IQ[a]	Verbal Learning[b]	Spatial Span Forward[c]	Spatial Span Backward[c]	Learning Error (displacement score)[d]
1	M	56	114	<5	6	6	45
2	M	57	118	<5	5	3	28
3	M	50	91	<5	6	6	82
4	M	67	103	<5	6	6	57
5	M	45	105	<5	5	6	136
6	F	50	98	<5	5	5	102
7	F	60	111	<5	5	5	41
8	F	64	104	<5	4	5	58
9	M	65	127	<5	6	6	26
10	M	64	89	<5	5	4	74
11	M	57	84	<5	5	4	85
12	M	64	99	<5	5	5	47
13	M	60	103	<5	5	6	57
14	M	68	93	<5	4	4	84
15	M	58	94	<5	6	5	36
16	M	49	84	<5	4	6	21
17	F	55	108	<5	5	6	23
18	M	56	81	<5	5	5	90
19	F	71	93	<5	5	4	101
20	M	74	81	<5	4	3	99
		M =59.5	M=99.0		M=5.1	M=5	M=64.6
		SD = 7.7	SD=12.7		SD=.7	SD=1	SD=32.1

Note. N.A. = not available, M = Male, F = Female, IQ = Intelligence Quotient, M = Mean, SD= Standard Deviation,

[a] IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

[b] Percentile scores for the total performance on the first five learning trials, measured with the Dutch version of the Rey Verbal Learning Test, for measurement of long-term memory (Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005).

[c] Corsi Block-Tapping Test, reflecting visuospatial memory (Kessels et al., 2008).

[d] Learning error (displacement score) was calculated for the Location Learning Test (Bucks, & Willison, 1997; Kessels, et al., 2006). Learning error in the reference group was M=8.1, SD=6.6.

7

Results for the Route Learning Tasks

Multivariate GLM showed a significant overall group effect (*F(6,31) = 5.0, p < .01,* η_p^2 = .490), suggesting that healthy controls performed better than KS patients. Scores per task are displayed in Table 3.

Table 3. Mean scores (SD) of the intentional and incidental group on the six spatial navigation tasks for the Korsakoff's syndrome patients (n=20), control subjects (n=20) and chance condition (n=15). Chance performance was calculated by asking a group of healthy controls to perform the tasks without having experienced the original route.

	Korsakoff's patients		Healthy Controls		Chance condition
	Intentional Condition	Incidental Condition	Intentional Condition	Incidental Condition	
Landmark recognition task (percentage correct *M*, *SD*)	53,1% (11.9%)	53.1% (14.5%)	64.4% (8.4%)	57.5% (8.7%)	45.8% (0.1%)
Landmark ordering task (*M*, *SD*)	4.2 (2.7)	4.3 (1.3)	4.4 (2.3)	3.7 (2.8)	3.1 (2.6)
Route time estimation task (absolute difference in minutes; *M*, *SD*)	5 (3.8)	7.3 (6.4)	2.6 (2.2)	2.2 (2.2)	13.9 (8.4)
Route distance estimation task (absolute difference in meters; *M*, *SD*)	547.5 (577.2)	465 (508.8)	210 (166.3)	350 (253.6)	1246 (1133.3)
Map Drawing Task (*M*, *SD*)	12.6 (9.4)	14.8 (11.1)	24.9 (5.7)	15.0 (4.8)	5.1 (5.1)
Route Walking Task (*M*, *SD*)	11.7 (.8)	12.3 (1.3)	14.2 (.6)	13.1 (1.4)	10.1 (1.4)

Note. *M*, mean; *SD*, standard deviation

Between-subject effects for the different tasks separately showed that the healthy controls performed better than the KS patients on the landmark recognition task (*F(1,36) = 4.9, p = .033,* η_p^2 = .120), the route time estimation task (*F(1,36) = 8.6, p = .006,* η_p^2 = .193), the map drawing task (*F(1,36) = 5.9, p = .021,* η_p^2 = .140) and the route waking task (*F(1,36) = 22.9, p < .001,* η_p^2 = .389), suggesting that performance of KS patients was hampered on a majority of route learning tasks. Both groups performed comparably on the route distance estimation task (*F(1,36) = 3.1, p = .089,* η_p^2 = .078), suggesting that specific aspects of route learning are relatively preserved in KS. Performance on the landmark ordering task was comparable in both groups (*F(1,36) = .1, p = .787,* η_p^2 = .002), but performance was very low in both groups. Performance was equal for both learning conditions on all subtasks (*ps >.14;* η_p^2 <.06). Moreover, the intention to learn did not modulate the performance on the landmark recognition task ($F(1,36) = .95, p = .336, \eta_p^2 = .026$), the landmark ordering task ($F(1,36) = .30, p = .589, \eta_p^2 = .008$), the route time estimation task ($F(1,36) = 1.1, p = .299, \eta_p^2 = .030$), or distance estimation task ($F(1,36) = .74, p = .396, \eta_p^2 = .020$). Importantly, however, there was a significant Group x Condition interaction on the map drawing task ($F(1,36) = 5.5, p = .025, \eta_p^2 = .133$) and the route walking task ($F(1,36) = 6.1, p = .018, \eta_p^2 = .145$), showing that the intention to learn modulated the performance on both tasks discrepantly in the patient and control group. Post hoc ANOVAs did not reveal an effect of gender ($ps > .37; \eta_p^2 < .03$)". Moreover, post hoc ANOVAs were performed for the map drawing task and the route walking task for both groups separately, to scrutinize the significant Group x Condition interactions. In the control group, the intention to learn was beneficial for both the map drawing task ($F(1,19) = 17.6, p = .001, \eta_p^2 = .495$) and the route walking task ($F(1,19) = 29.2, p = .041, \eta_p^2 = .212$). For the patient group, the intention to learn was not beneficial for the map drawing task ($F(1,19) = .23, p = .637, \eta_p^2 = .013$) or the route walking task ($F(1,19) = 1.6, p = .221, \eta_p^2 = .082$).

Results for the Control Experiment

KS patients performed significantly better than the chance group on the route time estimation ($F(1,33) = 11.1, p = .002, \eta_p^2 = .251$), route distance estimation ($F(1,33) = 6.6, p = .015, \eta_p^2 = .168$), map drawing task ($F(1,33) = 9.2, p = .005, \eta_p^2 = .219$) and the route walking task ($F(1,33) = 19.8, p < .001, \eta_p^2 = .375$), but not the landmark recognition ($F(1,33) = 3.8, p = .061, \eta_p^2 = .102$) and ordering task ($F(1,33) = 2.0, p = .163, \eta_p^2 = .058$). The results indicate that although KS patients are impaired on a majority of route learning tasks, performance is still better than chance level on four of the six tasks on route learning. Implications of this finding are elaborated below in the discussion. Healthy controls performed significantly better than the chance group on the route walking task ($F(1,33) = 62.2, p < .001, \eta_p^2 = .653$), map drawing task ($F(1,33) = 46.3, p < .001, \eta_p^2 = .584$), route time estimation ($F(1,33) = 34.4, p < .001, \eta_p^2 = .510$), landmark recognition ($F(1,33) = 27.0, p < .001, \eta_p^2 = .450$), and the route distance estimation ($F(1,33) = 14.1, p = .001, \eta_p^2 = .299$), but not the ordering task ($F(1,33) = 1.1, p = .300, \eta_p^2 = .032$). The results indicate that specifically the ordering task was too complicated for all participants.

Discussion

The aim of the present study was to assess to what extent KS patients can acquire spatial information during spatial navigation despite the presence of amnesia. Furthermore, we examined whether any residual acquisition in KS was based on automatic or effortful coding processes. Compared to the results of a matched control group KS patients showed hampered performance on the landmark recognition task, the route time estimation task, the map drawing task and the route walking task after walking a route through a residential area. Importantly, performance was relatively spared on the route distance estimation task. Moreover, in KS performance was superior on the route time and distance estimation tasks, the map drawing task and the route walking task compared to a chance group consisting of healthy individuals who performed the spatial tasks without actually ever having walked the route. The results of the current study clearly show that KS patients still acquire spatial information during navigation, although they are hampered on a majority of route learning tasks compared to healthy controls. With respect to the underpinning of residual acquisition in KS, the present results suggest that acquisition in KS is automatic rather than effortful, since no significant differences were obtained between the incidental (automatic) and intentional (effortful and automatic) condition for any of the route learning components, whereas for the healthy controls the intention to learn was beneficial for the map drawing task and the route walking task.

This is the first case-controlled study to investigate whether residual acquisition of information relevant to spatial navigation is present in KS. Earlier studies have already indicated that despite the presence of amnesia, KS patients are still able to benefit from repeated presentation of spatial configurations in faster detection of stimuli (Oudman et al., 2011; Postma et al., 2008). Conversely, an important difference between previous studies on repetitions of spatial information and the current study is that our study focused on the acquisition of spatial information in a real-life navigation experiment, instead of a computer paradigm on retrieval of contextual information. The results of the current study therefore extend findings of preserved contextual acquisition in KS to real-life navigation, but also indicate that acquisition occurred in KS after just one exposure of the route. Both findings are relevant to the study of contextual learning in KS, since there is profound damage to memorizing contextual information (Kessels et al., 2000).

One of the remarkable findings of the current study is that distance estimation was relatively spared in the KS group, whereas time estimation was clearly hampered compared to a control group. A possible explanation for this finding is that distance estimations are more dependent on kinesthetic and motor-learning than time estimation. Support for the view that distance estimations are moderated by kinesthetics is given by studies that suggest that distance estimations in virtual environments are systematically underestimated when there is no body movement or perceived control of body movement (Waller and Richardson, 2008; Von Stülpnagel and Steffens, 2013). Patients with Parkinson's disease do underestimate distances in their environment, possibly due to a lack of kinesthetic feedback following damage to the striatum of the brain (Demirci, Grill, McShane, & Hallett, 1997). Recent studies suggest that implicit motor-learning is relatively preserved in KS when the task at hand does not require multiple motor operations (Van Tilborg, Kessels, Kruijt, Wester, & Hulstijn, 2011), thus allowing the possibility of spared distance estimations based on motor learning. Nevertheless, the finding of preserved distance estimations should be interpreted with caution because of large variations in both the patient and control group.

Interestingly in the current study it was found that KS patients performed better than a chance group on route time and distance estimation tasks, a map drawing task and during actual route walking. With respect to actual route walking, the results of the current study are in line with a previous study on repeated route walking in KS (Kessels et al., 2007). In this study, ten patients with KS walked two routes five times following two teaching techniques. In a test phase KS patients scored better than chance level (about 3 out of 18 possible errors). Importantly, the current results show that even after passing the route once, KS patients performed better than chance level walking the route, although their results were deteriorated compared to a matched control group. This suggests that despite the presence of amnesia, route learning is still possible to some extent in, KS patients.

Regarding a better than chance level performance on time estimations, the finding of some residual ability to estimate time is in line with earlier research on estimating time intervals in KS and patients with frontal lesions (Mimura, Kinsbourne, & O'Connor, 2000). In their study, frontal lesion patients were less accurate than KS patients in estimating time intervals, who in turn were outmatched by control participants. The authors suggested that both episodic and working memory play a role in time estimations. An important difference between the current results and the results of Mimura et al. (2000) is that KS patients in our study all overestimated the time, while the patients in the earlier study tended to underestimate the time intervals. A possible explanation for this finding is that patients in the current study had to estimate the time they walked a route. In an earlier study patients had to estimate an interval between two stimuli without performing any other action. Earlier research on implicit motor learning suggested that motor sequence learning is relatively preserved when the task at hand does not require multiple motor operations (Van Tilborg et al., 2011). This could possibly contribute to the discrepancy between time estimations in the current study and an earlier study (Mimura et al., 2000).

In the current experiment, KS patients performed better than a chance group on a map drawing task, but were clearly hampered compared to a healthy control group. Moreover, healthy controls performed better on a map drawing task if they intended to remember the route. This is the first study to investigate drawing a route on a map in KS. Earlier evidence on patients with unilateral temporal lobectomy revealed that patients with right hemispheric temporal lobectomy and to a lesser extent left hemispheric temporal lobectomy show problems in drawing a map of a previously learned route (Spiers, Burgess, Maguire, Baxendale, Hartley, Thompson, & O'Keefe, 2001). Moreover, a study on the effects of intentionality on spatial navigation also showed that specifically the map drawing task requires intentionality for good performance (Van Asselen et al., 2006). The results of the current controls replicate this finding. Based on the studies by Spiers and colleagues (2001) and Van Asselen and colleagues (2006) one could conclude that intentionality, but also intact episodic memory is required for effective map drawing. Nevertheless, the KS patients in the current experiment outperformed a chance group, suggesting that besides an intentional and/or episodic memory system also an automatic memory system contributes to effective map drawing. This finding contradicts the opinion that learning in KS is restricted to mere priming-effects (Hayes et al., 2012).

The current results have practical implications for the diagnosis and rehabilitation of route learning in KS. An earlier study already indicated that patients with KS are able to increase task performance on a route walking task after repeated exposure to the route (Kessels et al., 2007). Our results extend this finding by suggesting that patients with KS are able to reasonably perform a route walking task after single-shot exposure to the route, while the recognition and ordering of landmarks is vastly compromised.

In the diagnostic phase of KS, this indicates that instead of focusing on performance on neuropsychological tests for long-term memory to predict route learning, it is relevant to actually test the ability to remember routes in patients with KS. Currently, numerous patients with KS are placed in closed long-term care facilities without the opportunity to leave the clinic, while current evidence indicates that patients with KS might be able to learn new routes despite their global amnesia.

It is likely that the basal ganglia contributed to acquisition of preserved route learning in KS. Recent studies show that the basal ganglia are of critical importance for acquisition of contextual information from our surroundings without conscious awareness, since patients with Parkinson's disease or Huntington's disease show no evidence for implicit contextual learning, while this form of learning is intact in KS (Van Asselen, Almeida, Andre, Januário, Gonçalves, & Castelo-Branco, 2009; Oudman et al., 2011; van Asselen, Almeida, Júlio, Januário, Campos, Simões, & Castelo-Branco 2012). Neurological damage in KS is found in the diencephalic structures of the brain (Kopelman, 2002). It is, therefore, likely that damage to these brain structures contributed significantly to the severely hampered performance on explicit measures of route learning.

In the current experiment, task performance on the landmark recognition task was low in KS patients and healthy controls. We assume that buildings in the environment did not differ much in saliency, contributing to this poor performance on landmark recognition.

There are some methodological considerations that have to be taken into account in the interpretation of the present findings. In the experiment, we did not want to give any cue to the participants in the incidental condition about the true aim of the study, so we chose not to measure time or walking speed. The experimenter tried to keep a standard walking gait for all participants that was practiced before the experiment took place. We assume that by keeping a standard walking gait there were minimal differences in walking speed between groups that could not explain the large task performance differences between groups.

For practical reasons we chose to perform the route learning task in the neighborhood of the institute. None of the patients or control participants mentioned familiarity with the residential area after explicitly being asked by the experimenter (admittedly there is a high chance that patients would have forgotten if they had). We can be confident that familiarity with the environment was limited in the patients, since it is the institute's policy to not allow outside exploration without specific authorization to do so.

It could be argued that the number of patients in the current study is relatively small, having negative implications for the statistical power in the experiment. We would like to stress that the number of participants in the current study does not differ from earlier studies on spatial navigation (e.g. Van Asselen et al., 2006). In a recent review on implicit learning KS only a small minority of studies included more than 10 KS patients (Hayes et al., 2012). We suggest that our results require replication in larger samples of KS patients. Moreover, the results of the current study limit to the specific group of KS patients as a recent study suggests that acquisition during spatial navigation is compromised to a larger extent in dementia (Kessels, Van Doormaal, & Janzen, 2011).

In conclusion, the results of the present study indicate that KS patients could acquire spatial information during spatial navigation, although task performance is generally deteriorated compared to healthy controls. Distance estimations of the route are intact and performance on time estimations of the route, map drawing task and route walking task were better than chance levels. Acquisition of spatial material in KS was irrespective of the intention to learn. The current study suggests that despite the presence of amnesia, patients with KS have a residual memory potential to acquire spatial information during spatial navigation.

Chapter 8

Procedural learning and memory rehabilitation in Korsakoff's syndrome a review of the literature

Published as:
Oudman, E., Nijboer, T.C.W., Postma, A., Wijnia, J.W., Van der Stigchel, S. (2015). Procedural learning and memory rehabilitation in Korsakoff's syndrome - a review of the literature. *Neuropsychology Review*, *25*, *134-148*. DOI: 10.1007/s11065-015-9288-7

Author Contributions: All contributing authors designed the research and wrote the review paper, EO conducted the literature search.

Abstract

Korsakoff's syndrome (KS) is a chronic neuropsychiatric disorder caused by alcohol abuse and thiamine deficiency. Patients with KS show restricted autonomy due to their severe declarative amnesia and executive disorders. Recently, it has been suggested that procedural learning and memory are relatively preserved in KS and can effectively support autonomy in KS. In the present review we describe the available evidence on procedural learning and memory in KS and highlight advances in memory rehabilitation that have been demonstrated to support procedural memory. The specific purpose of this review was to increase insights in the available tools for successful memory rehabilitation and give suggestions how to apply these tools in clinical practice to increase procedural learning in KS. Current evidence suggests that when memory rehabilitation is adjusted to the specific needs of KS patients, this will increase their ability to learn procedures and their typically compromised autonomy gets enhanced.

Introduction

Korsakoff's syndrome (KS) is a chronic neuropsychiatric disorder that is caused by thiamine deficiency. In the industrialized world, the most common cause of thiamine deficiency is alcoholism, with around 90 % of the deficiencies associated with alcohol abuse (Harper et al. 1986; Thomson et al. 2002; Kopelman et al. 2009). Interestingly, around 15 % of the chronic alcoholics have neurological signs of KS (Kril and Harper 2012). The most essential symptom of KS is a profound declarative memory impairment for learning and remembering new material (anterograde amnesia). In KS, there is also a temporally-graded memory deficits for remote memory (retrograde amnesia) which characteristically extends back many years or decades (Kopelman et al. 1999). Commonly, executive deficits are present, such as problems with inhibition of behavior, high interference of information sensitivity, poor judgment, poor planning abilities, problem solving inabilities, and perseverative responses (Van der Stigchel et al. 2012; Oscar-Berman 2012). The cognitive problems in KS are caused by diencephalic atrophy of the brain, with damage to the anterior nucleus of the thalamus, the mammillary bodies and the corpus callosum as the most common features of KS that are not caused by the direct neurotoxic effects of alcohol (see Fig. 1 for the anatomical localization of the most common brain abnormalities in KS). (Paller et al. 1997; Kopelman 1995; Kopelman 2002; Sullivan and Pfefferbaum 2009; Kril and Harper 2012; Pitel et al. 2012; Jung et al. 2012).

KS is usually preceded by an acute neurological condition called Wernicke's Encephalopathy, although in some cases KS seems to develop insidiously. Recent studies suggest that the most common symptom of Wernicke's Encephalopathy is the change in mental status, frequently presenting itself as a delirium (Wang and Hazell 2010; Wijnia and Oudman 2013). Strikingly, in the acute phase memory problems are not necessarily present but will develop over the course of the syndrome (Isenberg-Grzeda et al. 2012). Severe cognitive problems are often the direct consequence of undertreated thiamine deficiency (Oscar-Berman et al. 1982; Sechi and Serra 2007; Oudman et al. 2014). In the chronic phase of KS, cognitive problems do not respond to thiamine therapy any more (Smith and Hilman 1999). The diagnosis of KS requires extensive neuropsychological and neuropsychiatric examination to establish whether explicit memory impairment is disproportionate and can only be made with certainty after at least 6 weeks of sobriety, but could effectively require more time when serious somatic conditions are present (Kopelman 1995; Day et al. 2004).

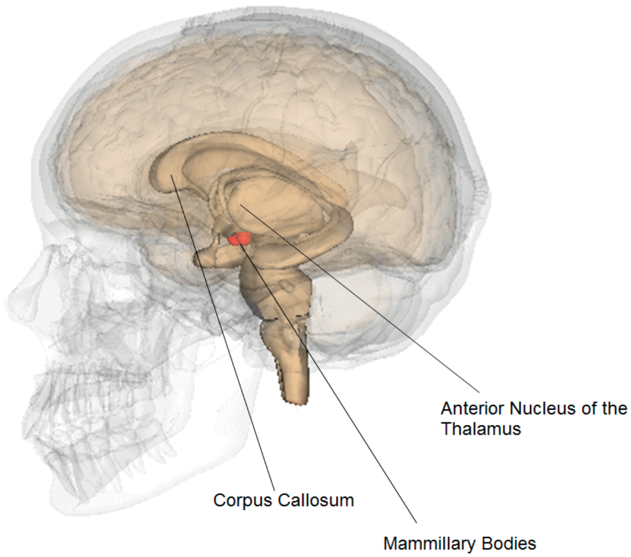


Figure 1. Neuronal loss in the Mammillary Bodies, the Corpus Callosum and the Anterior Nucleus of the Thalamus is common in patients with Korsakoff's syndrome. Modified and reprinted from Anatomography under Creative Commons Attribution.

Memory difficulties are a defining characteristic of KS (Kopelman et al. 2009). Currently, it is clear that memory difficulties in KS are most profound in declarative memory ("knowing what"), while procedural learning ("knowing how") is more preserved in KS (Squire 2004; Oudman et al. 2011). The acquisition of a skill or procedure occurs over the course of practice and is mainly thought to be nondeclarative. Because of the severity of the problems regarding "knowing what" in KS patients, many patients are in need of lifelong care (Oudman et al. 2013; Gerridzen and Goossensen 2014). Despite the severe problems it is intriguing to see that patients with amnesia sometimes show preserved learning abilities for learning skills and procedures ("knowing how"). In the literature, it is debated, both from a clinical and experimental perspective, whether procedural memory is fully spared or weakened (Hayes et al. 2012). From a clinical perspective, residual procedural learning would be relevant to the memory rehabilitation of individuals with KS, since this would indicate that patients with severe amnesia still can learn and rehabilitate in specific instances, and as such it might reduce their functional disability (Svanberg and Evans 2013; Horton et al. 2014). In the first part of the present review we detail the available evidence on motoric and cognitive procedural learning and memory in KS. In the second part we highlight the advances in memory rehabilitation which have been found to support procedural memory. Finally, we discuss how memory rehabilitation techniques can specifically support procedural learning in KS.

Procedural learning in Korsakoff's syndrome

Motoric procedural learning in Korsakoff's syndrome

The most typical example of procedural learning is motoric procedural learning or motor skill learning. The tradition to study motoric memory and learning in KS at least partially stemmed from investigations of the bilateral hippocampal patient H.M. who was still able to learn simple motoric tasks, despite his global amnesia (Scoville and Milner 1957). In his book "Deranged memory", George Talland (1965) defined the general aspects of procedural memory in KS. He was one of the first to note that also patients with KS are able to quickly learn a simple repetitive motor-task, such as how to use a plunger device to pick up small beads. Ever since this discovery, several paradigms have been adopted to assess motoric procedural learning in KS with variable outcomes throughout the long history of this field of research.

Rotor Pursuit and Mirror drawing

In the early days of studying motoric procedural learning the most applied paradigm was the pursuit rotor task. In a typical pursuit rotor task the participant was asked to maintain contact between a stylus and a metallic target on a moving turntable, while the turntable moved 45 rounds a minute. The first experiment on motoric procedural learning in KS was performed by Cermak et al. (1973). In their study, nine patients with KS and nine controls were fully able to learn and maintain the pursuit rotor task, suggesting that this form of motoric procedural learning is preserved in KS. The authors reasoned that pursuit rotor learning in KS is intact because there are no verbally mediated choices in this task whereas patients with KS would have large impairments on tasks that require verbally mediated choices. Despite the age of this paper, it is one of the few papers on motoric procedural learning in KS that included a group of healthy controls and it is therefore still relevant to the study of motoric procedural learning. Three years later, an experiment by Brooks and Baddeley (1976) showed complementary results to the Cermak study (1973). Importantly, Brooks and Baddeley (1976) additionally showed that pursuit rotor learning was still preserved after 1 week without practice. Later, Heindel et al. (1988) also demonstrated intact pursuit rotor learning in their amnesic group compared to patients with Huntington's disease who were severely impaired on the task. This study suggested a critical involvement of the basal ganglia in motoric procedural learning, since Huntington's disease is associated with basal ganglia damage whereas KS is not. This finding was later elaborated on by McEntee, Mair and Langlais (1987). Their study focused on the involvement of neurotransmitters in motoric learning by means of a rotor pursuit task and a mirror tracing task. In the mirror tracing task patients had to trace the outline of an object, a six-pointed star, while looking into a mirror. After the experiment, which showed increased performance, the cerebrospinal fluid of the patients was verified for levels of norepiphrine, serotonine and dopamine metabolites. Task performance on two tasks correlated moderately positively with the dopamine metabolite (HVA), suggesting a dopamine involvement to motoric procedural learning in the mirror drawing and the pursuit task. In conclusion, studies on rotor pursuit tasks suggest that this specific form of motoric procedural learning is fully spared in KS.

Serial Reaction Time and recent motoric tasks

In the late 80s of the last century, a different paradigm became popular, namely the serial reaction time paradigm. In a classical serial reaction time paradigm participants are seated facing a monitor and a response board below the monitor. On the response board four keys are arranged in a row. Participants are asked to press the key that is below the location in which an asterisk appears one of four locations on the monitor. A sequence is repeated throughout the experiment and reaction times on elements of this sequence are compared with reaction times to random elements. In contrast to the pursuit rotor tasks, the serial reaction paradigm does not require fine motor skills that could possibly hamper task performance on the pursuit rotor task. Also, the serial reaction paradigm makes it possible to measure reaction times as well as task accuracy. Recently, the serial reaction time paradigm has been put forward as a procedural task in three meta-analyses (Lum et al. 2014; Clark et al. 2014; Foti et al. 2015). An important aspect of the serial reaction time paradigm is the implicit nature of the learning effect: participants do not report that sequences are repeated during the task (Seger 1994). In the serial reaction time task Nissen and Bullemer (1987) investigated motor-sequence learning in KS patients. KS patients showed the same speeding curve for the repeated sequences, although they were slower than the controls and made more errors in the first blocks, suggesting that motor-sequence learning on this specific task is still spared in KS despite slower response times. Subsequently, Van Tilborg et al. (2011) showed comparable results as Nissen and Bullemer (1987), but found no evidence of less accurate response. Their study included 20 KS patients and 11 control subjects, making it the largest currently available study on motoric procedural learning in KS (Table 1).

Table 1. Summary of results of experimental studies on motoric procedural learning in Korsakoff's syndrome

Author	Year	Sample	Task	Outcome
Cermak et al.,	1973	9 KS 9 ALC 9 HC	Pursuit rotor Maze test	KS patients showed intact acquisition of the pursuit rotor task, but their acquisition of the maze task was less pronounced than in HC and AC.
Brooks &Baddeley	1976	3 KS 2 ENC 5 HC	Pursuit rotor Maze test	KS and EC patients showed intact acquisition of the pursuit rotor task. Their acquisition of the maze task was diminished compared to HC. Performance was retained in all groups after one week.
Heindel, et al.	1988	2 KS 1 ANO 1 INF 10 HD 10 AD 10 HC	Pursuit rotor	The KS, IN and AD patients showed preserved motor skill learning, while the patients with HD showed no evidence of learning.
McEntee et al.,	1987	8 KS	Pursuit rotor Mirror tracing	KS patients learned both tasks and their increase of performance related to dopaminergic activity.
Nissen & Bullemer	1987	6 KS 8 HC	Serial reaction time	KS patients were slower and less accurate than HC, but learned the serial reaction time task.
Nissen et al.	1989	7 KS 8 ALC 7 HC	Serial reaction time Maze task	KS patients learned and maintained the serial reaction time tasks and maze task, but failed to accomplish the same amount of learning on the maze task. Performance was preserved after one week.
Van Tilborg et al.	2011	20 KS 11 HC	Serial reaction time task	KS patients were slower than HC, but learned the serial reaction time task with the same amount of errors.
Swinnen et al.	2005	11 KS 11 HC	Arm coördination task	KS learned and maintained less than HC, but were better able to do so when feedback was provided.

Note. KS = Korsakoff's syndrome; ALC = Alcoholics; HC = Healthy Controls; ENC = Encephalitic amnesia; ANO = Anoxia induced amnesia; INF = Cerebral infarction induced amnesia ; HD = Huntington's disease.

Nissen et al. (1989) applied the serial reaction time task and a maze task. The authors showed that the learned sequence in the serial reaction time task was retained over 1 week without training. The performance on the serial reaction time task was comparable in healthy controls, alcoholics, and KS patients, but performance on the maze task was deteriorated. The results on the maze tasks are more elaborately discussed below in the paragraph on spatial procedural learning. According to the authors, performance in the serial reaction time task is much more constrained than in unstructured tasks, such as the maze task. They argue that constraining the response selection is an essential element for motoric procedural learning in KS. This notion was later supported by

Swinnen et al. (2005). These authors developed a task that required coordination of the forelimbs such that one forelimb was 90° out-of-phase with the other, which is not a regular motoric action in daily life and therefore requires practice. Eleven KS patients and eleven healthy controls practiced for 2 days, with and without feedback on their coordination. The KS patients were able to learn and maintain the coordination task in the feedback condition, but showed less learning when feedback was withheld. According to the authors, the key to motoric memory preservation in KS is that perceptual information is made available to drive the motoric action.

Summary

In brief, there is abundant evidence that patients with KS are able to learn motoric procedures, often at the same rate and level of performance as healthy controls. Initial studies on the pursuit rotor task that suggested that all forms of motoric procedural learning are intact in KS were later nuanced by findings on the serial reaction time task. In the serial reaction time task, KS patients were slower than the controls and made more errors in the first learning blocks, suggesting that motor-sequence learning is not fully intact but spared to a reasonable extent. In order to be able to exert effective coordination in a novel movement task, KS patients seem to require feedback to enhance procedural learning. The quality of the available evidence on motoric procedural learning is restricted due to the relatively small sample sizes and the lack of control participants in many studies. Nevertheless, it is important to note that even in experiments that showed hampered task performance in KS compared to healthy controls, still evidence was reported for spared motoric learning potential.

Cognitive procedural learning in Korsakoff's syndrome

A discrepant form of procedural learning is cognitive procedural learning. Cognitive procedural learning involves the learning of a strategy or a procedure to perform a cognitive skill. In contrast to motoric procedural learning do these skills not necessarily require a motoric response, but rather require the mastering of a law or algorithm that requires cognitive reflection. One could argue that cognitive procedures do require more cognitive resources than motoric procedures leading to hampered task performance in KS.

Mirror reading and Visuoperceptual learning

A cornerstone paper by Cohen and Squire (1980) described cognitive procedural learning in the form of mirror reading. Mirror reading involves the procedural learning of a perceptual-verbal skill. Four KS patients, three patients with electroconvulsive therapy induced amnesia, one patient with acquired brain damage and six controls saw cards with three nouns reflected by a mirror. Subjects were asked to read the words out loud and press a button after finishing the trial. Half of the items were repeated throughout the experiment, the other half were not. There were five blocks of ten word triads on three consecutive days and one block after 13 weeks. Surprisingly, all subjects became quicker on nonrepeated trials and repeated trials, but the curve of acquisition was steeper for the repeated trials. In the group of patients with amnesia this effect was less pronounced than in controls, but it was still evident. The patients showed explicit memory problems for recognizing the presented words, but even after 13 weeks without training, the mirror-reading procedure was retained in KS as in healthy controls. The authors argue that there are clear-cut differences between the basal ganglia mediated nondeclarative learning and declarative learning. In two later studies, the findings of Cohen and Squire (1980) were replicated in eight KS patients (Martone et al. 1984) and one KS patient (Beaunieux et al. 1998). Both studies were case-controlled with ten healthy controls. These studies on mirror reading suggest that patients with KS are able to learn and maintain the ability to read mirrored words, but they require additional learning sessions compared to healthy controls and they do benefit less from word repetition. In a later study by Fama et al. (2006) four KS patients, nine alcoholic patients and twenty-one healthy controls were asked to identify two sets of incomplete pictures. Although patients became better in the identification of repeated stimuli, there was no transfer of learning to a different set of stimuli with a comparable level of difficulty, suggesting that learning appeared to occur at a stimulus level instead of a skill level.

Laws and algorithms

In quite a different paradigm, Wood et al. (1982) showed the learning of a Fibonacci's law by six patients. In this experiment patients had to predict numerical series based on the minimal amount of information that is need to predict Fibonacci's series. In Fibonacci's series, each next number is the sum of the two preceding numbers. There were three learning trials and two retention trials, one after 24 h and one after 17 weeks. Especially the latter trial was the longest interval between the test phase and the recall phase that was applied in any study on procedural learning. The KS patients showed a weaker learning curve than would normally expected by healthy control subjects, but strikingly the retention was just as good in the patients as in the controls. Moreover, there was a substantial gain in performance over learning sessions. A few years later, Charness et al. (1988) studied the learning of an algorithm to square two-digit numbers in KS. One patient and seven healthy controls were asked to learn the algorithm in seven sessions on seven separate days. The patient was able to actively apply the algorithm to square numbers at the same rate as healthy controls, but he was unable to state the algorithm when asked. He was also not able to deal with exceptions to the algorithm. The authors therefore argue that the algorithm for the KS patient could be applied in a compiled fashion: the first step leads directly to the execution of the next step. They state that the algorithm task is likely to be one of the most complex cognitive procedural skills with only the Tower of Hanoi tasks as being more difficult (Table 2).

Table 2. Summary of results of experimental studies on cognitive procedural learning in Korsakoff's syndrome

Author	Year	Sample	Task	Outcome
Cohen & Squire	1980	4 KS 1 ABD 3 ECT 6 HC	Mirror reading	KS, ABD and ECT patients acquired the skill at an equivalent rate as HC and retained it for three months.
Martone et al.	1984	8 KS 10 HD 10 HC	Mirror reading	KS, but not HD patients acquired the skill at a normal rate, but KS patients did not recognize the words while HD patients did.
Beaunieux et al.	1998	1 KS 1 ALC 10 HC	Mirror reading Tower of Hanoi	Both cognitive skills were learned at the same rate in KS as in HC and preserved after 1.5 hours.
Wood et al.	1982	6 KS	Fibonacci's law	All patients showed substantial gain of performance that was somewhat maintained after one day and seventeen weeks.
Butters et al.	1985	5 KS 1 TUM 1 ENC 15 HD 12 HC	Tower of Hanoi	KS, TUM, ENC and HD patients were impaired relative to HC. KS patients showed some evidence of learning.
Beaunieux et al.	2013	14 KS 15 ALC 15 HC	Tower of Toronto	10 KS were able to perform the task, but obtained lower results than both CS and AL.

Note. KS = Korsakoff's syndrome; ALC = Alcoholics; HC = Healthy Controls; ABD = acquired brain damage; HD = Huntington's disease; ECT= Electroconvulsive therapy induced amnesia; TUM = Brain Tumor; ENC = Encephalitic amnesia

Tower of Hanoi/Tower of Toronto

The Tower of Hanoi task was first applied in KS by Butters et al. (1985). Six patients with amnesia (5 KS, 1 amnesia patient with a brain tumor), 15 patients with Huntington's disease and 12 healthy controls participated in this experiment. In this Tower of Hanoi task subjects were asked to arrange five blocks according to size on one of three wooden pegs. They were not allowed to place a larger block on a smaller one. To solve the puzzle, the subjects had to move the blocks around with an optimal solution of 31 moves. Subjects were required to solve the task eight times on two consecutive days. The patients with amnesia and the patients with Huntington's disease failed to show the same improvement over learning trials as healthy controls. The authors argue that two factors could have contributed to the lack of finding improvement in KS: the Tower of Hanoi could have been a cognitive procedure that was too complex for the patients with severe memory disorders. Moreover, the Tower of Hanoi requires more cognitive abilities than the cognitive procedure of solving the puzzle. It also requires identification, sequencing and strategies to ensure an efficient solution. Later, the results by Butters et al. (1985) were questioned by Beaunieux et al. (1998). A patient with KS and ten healthy controls were able to learn an easier version of the Tower of Hanoi with three discs (optimal solution in seven moves) in the same amount of time as healthy subjects over three trials. After an interval of one-and-a-half hour performance was maintained. The authors argued that while the task was somewhat easier than in the study by Butters et al. (1985), the procedure was clear for the patient and it was not contaminated with other cognitive functions such as executive functioning or episodic memory which are compromised in KS.A recent study by Beaunieux et al. (2013) aimed to disentangle the contributions of cognitive procedural learning, working memory, executive functioning and declarative memory in the acquisition of the Tower of Toronto task. Fourteen KS patients, fifteen chronic alcoholics without Korsakoff's syndrome and fifteen controls performed the task with three pegs and four discs on four consecutive days. The KS patients made more errors and needed more time to solve the puzzle than the alcoholics and healthy controls, but learned to perform the task. According to the Adaptive Control of Thoughts Model (Anderson 1992), cognitive procedural learning occurs in three subsequent phases. Learning a new cognitive procedure requires highly controlled processes in the first phase, but less controlled process in the second and third phase (Beaunieux et al. 2006). The authors argue that specifically the first phase of cognitive procedural learning in KS requires more time than in healthy subjects. An important difference between the patients that showed intact procedural learning in the Tower of Toronto task and the patients that did not show procedural learning was the degree to which executive functioning was impaired.

Spatial procedural learning in Korsakoff's syndrome

Spatial memory is vitally important in everyday life. Without this type of memory we would constantly get lost, loose our belongings and we would not be able to make plans to navigate to any place. Spatial memory requires both declarative and nondeclarative aspects. Spatial procedural learning ranges from mediation of sensorimotor acquisition up to associations between environmental stimuli and responses (e.g., turning left at a central cross-point during navigation) (Passot et al. 2012). Both processes are involved in route learning and the learning of visuo-spatial regularities. The Maze task, the Spatial Pattern Learning Task, the Implicit Contextual Cueing Task and multiple forms of route learning and navigation have been applied.

Maze task
Already in the first experiment on procedural learning in KS, the maze task was adopted. In a typical maze task participants needed to find the exit of the maze with their index finger with four or six cross-points. Often the time to accomplish the task and the number of required turning points are measured as indices of task performance. Cermak et al. (1973) showed that patients were less able to learn the maze task than healthy controls. In their experiment, KS patients made more errors and required more time to complete the maze task than healthy controls. The authors argued that also the learning of a maze task could be verbally mediated, resulting in hampered task performance in KS. Later, Brooks and Baddeley (1976) showed complementary results to the Cermak study (1973). KS patients made substantially more errors than healthy controls on the maze task, but they were able to accomplish better performance over ten consecutive trials. Moreover, after 1 week, performance was retained to the same extent as in healthy controls. The results of this study suggested that KS patients were still able to learn a maze task and also maintain it for a prolonged period, but the amount of errors was higher in the patient group than in the control group. Also, Nissen et al. (1989) applied a tactual stylus maze task. In the tactual stylus maze task participants needed to perform two types of mazes over 35 trials. In the blocked maze the alleys were blocked by small pieces of Plexiglass, in the unblocked maze the alleys were not blocked. Both types of maze had ten choice-points

and were therefore more difficult than applied in earlier studies on maze learning in KS. KS showed an initial decrease of completion time from around 80 s in the first trial to around 40 s in the fifth trial. In the last 30 trials of the experiment, healthy subjects and alcoholic controls further increased their performance, but KS patients failed to do so. After 1 week, performance was not statistically significantly different from the last trial in KS patients. The results of this study suggest that KS patients could learn and maintain the maze task to some extent, but failed to learn in later trials. According to the authors, performance in the maze task is unconstrained which makes errors likely to occur in KS.

Spatial Pattern Learning Task

In the Spatial Pattern Learning Task, participants are required to move a cursor to one out of four circles on a screen. The participant needs to move the cursor to the target stimulus that turns red. Van Tilborg et al. (2011) showed that twenty patients diagnosed with KS and fourteen controls were able to move faster to the target when a pattern was repeated. Nevertheless, KS patients made more errors and showed less search facilitation than controls, showing evidence for a decline in spatial procedural learning in patients with KS. A number of participants noted that the sequences were not random, which could possibly have affected the results of the experiment. The authors argue that a strong spatial response component is the primary factor that resulted in less pronounced learning for patients with KS than healthy controls.

Implicit Contextual Cueing

Implicit contextual cueing is the ability to acquire contextual information from our surroundings without conscious awareness. In a typical implicit contextual cueing experiment, subjects need to find a target stimulus (a T) among distractors (Ls) during visual search. Some of the configurations of stimuli are repeated during the experiment resulting in faster responses than for novel configurations, without subjects being aware of their repetition. In our study on implicit contextual cueing, patients with KS were slower in responding than the matched controls, but the Implicit Contextual Cueing effect was similar in both groups. This results suggests that KS patients were able to learn repetitions of spatial configurations (Oudman et al. 2011). Importantly, both patients and healthy controls were not able to recognise the spatial configurations, suggesting that the process of spatial learning was implicit. The results of our study extend the results of Postma et al. (2008) on conscious and unconscious object-location memory. In their experiment, 23 patients had poor (explicit) memory for object locations in their natural surroundings. Strikingly, they performed slightly better than the controls on unconscious spatial memory, showing that unconscious and conscious influences of spatial memory are functionally distinct (Table 3). Route learning in KS was investigated by Kessels, van Loon, and Wester (2007). In their study, ten patients with KS had to walk two routes on the hospital terrain. In four sessions on four consecutive days the patients walked one of the routes. On one route, the experimenter asked the patient which way to go. The patient had to guess the correct answer, until the correct response was made. On the other route, the experimenter told the patient which way to go. Both errorless learning and trial-and-error learning resulted in equal spatial procedural learning. For the condition in which the patient was asked which way to go, participants showed a clear reduction of errors over the four consecutive learning sessions, suggesting that spatial procedural learning was preserved to some extent.

Table 3. Summary of results of experimental studies on spatial aspects of cognitive procedural learning in Korsakoff's syndrome

Author	Year	Sample	Task	Outcome
Postma et al.	2008	23 KS 18 HC	Object-location memory	Using the process dissociation procedure it became clear that KS and HC showed comparable influence of unconscious memory during an object-location memory task. After one week influence of unconscious memory was not affected.
Oudman et al.	2011	18 KS 20 HC	Implicit Contextual Learning	KS patients showed intact ability to to find a target among a number of distractors during visual search after repetition and without conscious recollection.
Van Tilborg et al.	2012		Serial reaction time task Pattern learning task	Implicit motor learning occurred in both groups of participants on the serial reaction time task; however, on the Pattern Learning Task, the percentage of errors did not increase in the Korsakoff group in the random test phase, which is indicative of less implicit learning.
Kessels et al.	2007	10 KS	Route learning task	Both errorless learning and trial-and-error learning supported a route learning task.

Note. KS = Korsakoff's syndrome; ALC = Alcoholics; HC = Healthy Controls; ABD = acquired brain damage; HD = Huntington's disease; ECT= Electroconvulsive therapy induced amnesia; TUM = Brain Tumor; ENC = Encephalitic amnesia

Summary

Although many studies demonstrate that patients with KS have some ability to learn cognitive procedures, the majority of studies show that performance in the learning phase is compromised compared to healthy controls. This deteriorated learning performance is, however, followed by a relatively preserved recall after a prolonged time for mirror reading (13-weeks in Cohen and Squire 1980) and learning the Fibonacci-law (17-weeks in Wood et al. 1982). The available research suggests that is likely that the complex tasks, such as in the Tower-Tasks, require multiple cognitive functions that are compromised in KS. Patients with KS are able to learn spatial regularities depending on the specific task at hand, but do not have maximum performance if the task requires multiple free response options without constraining or the instructions are normally verbally mediated such as in the frequently adopted maze task. Specifically in the acquisition-phase of a cognitive procedure, executive functions and elaborated working memory functioning are required. Nevertheless, the majority of research establishes that cognitive procedural learning is at least partially spared and well-preserved in KS.

Interim discussion

Remarkably, all the of the papers reviewed here have given evidence of procedural learning potential in KS, despite the large variety of studies that have been reviewed. However, if we look at the level of learning potential, there are discrepancies between paradigms and studies. For example, the KS patients showed the same amount of learning as healthy controls in the pursuit rotor paradigm, a specific instance of motor skill learning (Cermak et al. 1973; Brooks and Baddeley 1976; Heindel et al. 1988). On the opposite, there was much less procedural learning on the four disc Tower task, an instance of cognitive procedural learning, for patients with KS compared to healthy controls (Beaunieux et al. 1998, 2013). This discrepancy between both outcomes is, however, likely based on task complexity rather than the type of procedural learning, since also task performance on the motoric procedural Serial Reaction Time Task and movement feedback task was hampered in KS (Nissen et al. 1989; Swinnen et al. 2005). In the next paragraph we discuss whether and how memory rehabilitation techniques can facilitate learning potential in KS.

Rehabilitation of procedural memory in Korsakoff's syndrome

Since patients with KS can learn new procedures it is worthwhile to establish how memory rehabilitation techniques could facilitate procedural learning and memory in KS. Memory aids and assistive technology capitalize on intact aspects of procedural learning to support acquisition of new procedures (Wilson 2009). Such interventions can both be compensatory or supportive to procedural learning. Since both are relevant to successful memory rehabilitation in Korsakoff's syndrome, both types of interventions are reviewed in the second part of this manuscript. It is important to note that in the past decade the knowledge how to apply memory rehabilitation techniques to support procedural memory has increased to some extent, but the body of knowledge is still in its infancy. The available evidence concerns memory aids and interventions based on errorless learning. Both topics will be discussed separately in this paragraph.

Memory aids: the role of assistive technologies

The view that KS is a static condition that does not permit further recovery is a commonly held one (Smith and Hilman 1999). Fortunately, the number of papers that disregard this idea is growing and there is nowadays accumulating evidence that rehabilitation of memory is possible for KS (Svanberg and Evans 2013; Horton et al. 2014). In the recent years numerous case-studies and group-studies have been performed to investigate memory rehabilitation in KS. Rehabilitation for patients with KS tends to focus on two strategies that are sometimes combined in the intervention: the deployment of external memory aids and the use of Errorless Learning techniques (Kopelman et al. 2009). Currently, there are six case studies available that investigated the use of memory aids in KS. The first case study that investigated the use of an external memory aid to facilitate residual memory in KS was performed by Davies and Binks (1983). In one KS patient, prompt cards and leaflets were used by the experimenter and the wife of the patient in order to reduce the memory demands for the patient. It was essential for the patient that his wife would keep the prompt cards and leaflets up to date, but the patient was helped by the external memory aids. Associative cues at storage and retrieval could boost successful retrieval of information relevant for the KS patient to be more autonomous in daily life.

A study that incorporated traditional assistive technology in a holistic approach was performed by de Fatima Alves Monteiro et al. (2011). The authors described a 25-week neuropsychological rehabilitation program for a patient with KS. A weekly cognitive training session was accompanied with the use of assistive technology. The patient was learned to use notes, schedules, a week-program and a calendar over the course of the 25 weeks. Importantly, the patient in the case study was accompanied by two caregivers all day long for every day of the week. Both caregivers subjectively noted that memory failures in the patient were reduced by the intervention. In the behavioral descriptions of the caregivers it was verified that the patient resorted frequently to the appropriate use of memory aids. Here, assistive technology was helpful in a holistic rehabilitation approach, although the effectiveness of the memory aid was based on subjective reports rather than objective measures.

The first study on assistive technology that adopted an electronic aid was performed by Morgan et al. (1990). An electronic diary was used to improve the ability of a man with KS to attend therapy-groups. At the start of the project the patient was prompted by staff members until he had an attendance rate of 80 % in the 14th week of the experiment. At the 18th week the electronic diary was introduced that resulted in 100 % attendance to the groups, but this improvement was no longer significant since the average attendance rate was already relatively high and there was some variation in attendance between weeks. An important contribution of this study to the field on assistive technology in KS is that combinations of assistive technology and prompts by care members were applied that resulted in maximal attendance to an appointment.

More recently, de Joode et al. (2013) investigated the feasibility of the use of a personal digital assistant (PDA) to support prospective memory functioning in a patient with KS. The PDA in this study was more complex than a simple prompting device since the patient could enter his own appointments and add notes to the appointment. A virtue of this study, compared to the earlier studies on assistive technology in KS was that this study compared the use of a PDA with a simple memory watch and a time period without any assistive support. Three goals were formulated in this experiment, namely being on time, having a long-term goal (e.g., sending an email message at a certain time) and remembering to take medication. Due to absence of a number of valid observations it was difficult to discern a pattern in the outcome for the second and third goal. The main conclusion of the experiment was, however, that the PDA scored essentially the same as the memory watch on all three formulated goals, but both interventions had positive effects compared to the no aid condition. Both the patient and clinical staff members favored the PDA over the memory watch as an cognitive aid. Nine months after the experiment the patient was still primarily using the alarm function of the calendar for which he required supervision to keep the calendar up to date. The most recent study on assistive technology did not focus on prospective memory, but instead focused on remembering past events by use of assistive technology. In this study, a patient with KS was already able to make use of compensatory strategies through an agenda and prompts of family members (Svanberg and Evans 2013). A problem that still existed was that through her memory problem she had no longer evidence to support her sense of herself, resulting in mood problems. The SenseCam, a wearable, automatic camera was used to record five regular activities she performed. Originally, it was intended to have eight regular activities recorded, but the patient wanted to stop the experiment after some time. The images that were automatically made during the tasks were downloaded onto a laptop and the patient watched them each day. The subjective memory rating of the patient increased, but her mood did not change. The patient reported that "it was like watching someone else's life". The authors concluded that careful establishment of consistent support networks and normalization of the technology are useful to increase engagement and the SenseCam could be part of a holistic approach to memory rehabilitation in KS.

Table 4. Summary of results of clinical studies on the application of memory aids in Korsakoff's syndrome

Author	Year	Sample	Intervention	Outcome
Davies & Binks	1983	1 KS	Prompt cards and leaflets to reduce the memory demands for the patient	Cues at storage and retrieval boosted successful retrieval of information to be more autonomous in daily life.
Fatima Alves Monteiro et al.	2011	1 KS	A 25-week holistic neuropsychological rehabilitation program	The patient resorted frequently to the appropriate use of memory aids. No follow-up.
Morgan et al.	1990	1 KS	Electronic diary and verbal prompting to improve the ability to attend therapy-groups	Verbal prompting led to regular attendance of the therapy-groups, but the electronic diary could not further increase attendance.
de Joode et al.	2013	1 KS	Personal Digital Assistant (PDA) and memory watch to support being on time, having a long-term goal (e.g. sending an email message at a certain time) and remembering to take medication	PDA and memory watch supported being on time. Data on the other goals was missing. After the experiment, the patient stopped using the PDA and memory watch.
Svanberg & Evans	2013	1 KS	SenseCam, a wearable, automatic camera to record regular activities and support memory and mood	The experiment was stopped after five weeks. The patient reported increased subjective memory rating. Mood was not increased.

Note. KS = Korsakoff's syndrome

Summary

Over the past decades, the knowledge how to apply memory aids in KS has increased to some extent, but the body of research on assistive technology is still in its infancy. The available evidence from case studies suggests that assistive technology are most likely to have a positive effect when (1) the formulated goals are restricted, (2) there is much time available to guide the patient in the process of learning how to use the assistive technology and (3) when the use of assistive technology is combined with elaborated learning techniques or an element in a holistic approach. There is an absence of case-controlled research on the application of memory aids, but the available case studies suggest that KS patients still require assistance from a family member or therapist despite the successful use of a memory aid. It was quite striking that in at least two of the six case studies the intervention as planned was altered during the process because of the will of the patient or family members of the patient (de Joode et al. 2013; Svanberg and Evans 2013), which could be an inherent feature of rehabilitating a patient with KS.

Errorless Learning

Table 5. Summary of results of clinical studies on the application of errorless learning techniques in Korsakoff's syndrome.

Author	Year	Sample	Intervention	Outcome
Wilson et al.	1994	1 KS	Programming an electronic aid	The patient acquired the skill of entering information into an electronic memory aid. EL was more effective than TEL.
Komatsu et al.	2000	8 KS	Learning face-name relationships	KS patients learned face-name relationships over four consecutive learning sessions. The proportion of correctly learned names was higher in EL than in TEL.
Kessels et al.	2007	10 KS	Route learning	KS patients showed increased task performance on a route learning task over five consecutive sessions. EL and TEL were equally effective.
Oudman et al.	2013	16 KS	IADL learning	Both EL and TEL resulted in increased performance on the IADL over eight sessions, but in a follow-up after four weeks performance was only still elevated in TEL.

Note. KS = Korsakoff's syndrome ; EL = Errorless learning; TEL = Trial and Error Learning; IADL = Instrumental Activity of Daily Living.

8

Errorless learning is a well-known learning technique that has been applied successfully in KS among other groups of patients with cognitive disorders (see Clare and Jones 2008 for a critical review). The technique was originally developed by Terrace (1963). The most essential element of this learning technique is that the patient is not allowed to make errors by eliminating guessing during the process of learning, to support the already comprised memory functioning. Errorless learning is specifically relevant for patients with KS, since it is thought to be dependent on intact implicit learning (Clare and Jones 2008).

To date, four studies on errorless learning in KS have been performed. The quality of the available evidence is mixed and none of the studies was case controlled. One of the first case studies on errorless learning in neurological patients included a description of a patient with KS (Wilson et al. 1994). In two experiments, the patient acquired the skill of entering information into an electronic memory aid. The errorless learning technique was more beneficial than the control condition (trial-and-error learning), suggesting that errorless learning was supportive to the residual memory of the KS patient. The first group studies on errorless learning in KS were performed by Komatsu et al. (2000). In their experiment, eight patients diagnosed with KS performed four study conditions to learn fictitious face-name relations. Two study conditions were based on the principle of errorless learning (paired associate and vanishing cue) and two study conditions were based on trial-and-error learning (target selection and initial letter). For all study conditions patients were trained twice a week for 2 weeks. In the paired associate condition, patients had to say the name of the face they saw on the screen which was displayed below the person. In the vanishing cues condition, the name of the face was also shown, but gradually was removed over five trials. In the target selection condition, patients needed to select the name of the person from five alternatives until they chose the correct one. In the initial letter condition, patients had to guess the name of the person they saw. After four guesses the correct name was displayed on the screen. The authors argued that both the vanishing cues condition and the initial letter condition required more effort than the paired associate and target selection condition. The results of the experiment showed that KS patients had most benefit from both errorless conditions (paired associate and vanishing cues), but a week after the experiment there was a floor effect for all conditions. The authors suggested that more learning trials were required and performed an additional experiment to test this hypothesis in four of the patients from the initial experiment. Although an increase of the trials did also increase the correct responses in the errorless conditions, no discrepancy between effortful and effortless errorless learning became clear. In a later study, errorless learning was also compared to trial-and-error learning in ten patients with KS to study route learning (Kessels, van Loon, and Wester 2007). In this within-subjects design both learning methods were effective to learn a novel route, but errorless learning was not better than trial-and-error learning. The authors suggested that the nature of the learned material (route learning) is likely to determine the benefit of errorless learning. An important aspect that could have contributed to the finding of the study was that the error rates were quite low in both experimental conditions and that more learning trials were needed to accomplish the beneficial effect of errorless learning. This study did not include a follow-up after a prolonged period. Recently, we performed a study on the acquisition of an activity of daily living, namely performing the laundry (Oudman et al. 2013). In our between-subject experiment, 16 patients with KS learned how to perform the laundry using a washing machine. Both errorless learning and trial-and-error learning were equally effective during the eight learning trials, but after a month without performing the laundry, errorless learning was beneficial compared to trial-and-error learning (see Fig. 2).

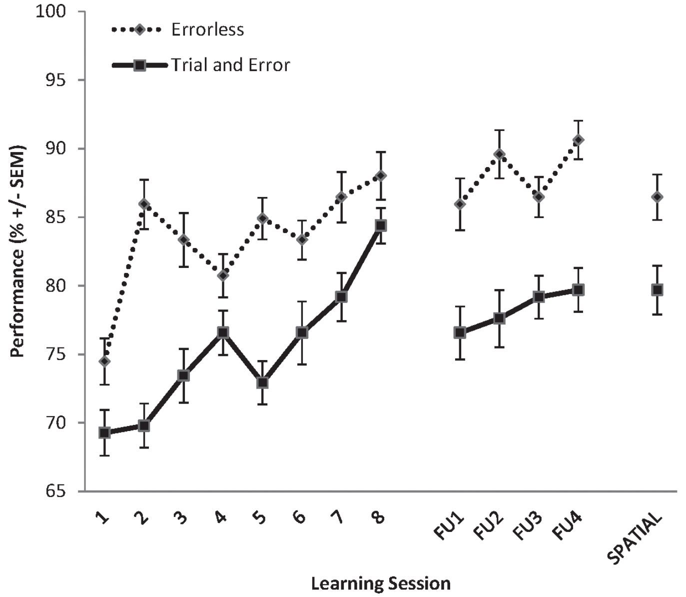


Figure 2. Performance on each learning session for Korsakoff's syndrome patients in the errorless learning (n=8) and trial and error learning (n=8) condition. For total score comparisons, the total scores per session were adjusted to a 100-point scale. The sessions "FU1-FU4" represent a follow up after four weeks without training. The "Spatial" session was performed in a different spatial layout.

In the last session the spatial lay-out of the scene was changed. Performance in the errorless learning condition then deteriorated. The main finding of this study was, however, that errorless learning is a feasible technique for (re) learning an instrumental activity of daily living that could still be beneficial after a period without training.

8

Summary

There are currently four studies available on the effectiveness of errorless learning as a learning technique to learn new material or procedures in KS. Although the results are mixed, it is safe to say that errorless learning is beneficial compared to trial-and-error learning for some learning situations, such as learning names or procedural skills (Wilson et al. 1994; Komatsu et al. 2000; Oudman et al. 2013). Moreover, even if it is not more effective than trial-and-error learning it is effective (e.g., leading to a reduction of errors) to have a structured stepwise learning schedule (Kessels et al. 2007). Although it has been suggested that errorless learning is specifically effective for procedural learning, the beneficial effects of errorless learning are not only restricted to procedural tasks but also support name learning. Both verbal cueing and modeling seem relevant to the learning potential. The quality of the experiments on errorless learning is mixed and case-controlled studies are required. Importantly, the application of errorless learning always requires skilled therapist and is time-consuming. Although residual learning in KS is possible, errorless learning techniques are likely to result in fixed patterns of behavior that could not easily be manipulated (Oudman et al. 2013).

Discussion

The aim of this review was to describe the available evidence on procedural learning, to highlight the advances in memory rehabilitation, and to discuss how memory rehabilitation techniques successfully may support procedural learning in KS. We evaluated 17 studies on procedural learning in KS and 9 studies on memory rehabilitation in KS, dating from 1976 to 2013. Based on the literature, there is substantial evidence that patients diagnosed with KS are able to learn procedural tasks and often even reach normal levels of task performance. Memory rehabilitation techniques for KS have been investigated in case studies and small-scale group studies, therefore the question how memory rehabilitation techniques can facilitate procedural learning in KS could only be answered tentatively. There is a specific hiatus concerning clinically relevant rehabilitation programs for KS. Based on our current review, we recommend that more rigorous, randomized, case-controlled studies are essential to develop a better understanding how memory rehabilitation can facilitate procedural learning in KS.

What could hamper procedural learning in Korsakoff's Syndrome?

For certain procedural tasks, such as the pursuit rotor task or the serial reaction time task, procedural learning is fully preserved and maintained in KS after intensive practice (Cermak et al. 1973; Brooks and Baddeley 1976; Heindel et al. 1988; Nissen et al. 1989). For other procedural tasks, such as the Tower task and the maze task, learning performance is evident but reduced compared to healthy controls (Cermak et al. 1973; Brooks and Baddeley 1976; Nissen et al. 1989; Butters et al. 1985; Beaunieux et al. 2013). There are a number of interrelated explanations for protracted procedural learning in KS given in the literature. A first explanation relates to the cognitive preconditions for procedural learning that are not fulfilled in KS, a second explanation refers to the number of constrains during the procedural task at hand, and a final explanation focuses on the amount of feedback that is given after (un) successful procedural task performance. We will discuss each explanation briefly.Cermak et al. (1973) already found compromised procedural learning on the maze task and intact procedural learning on the pursuit rotor task. The authors explained that one could learn how to perform a maze task by remembering a sequence of left-right responses with the aid of verbal cues, but for the pursuit rotor-task this is not possible, probably resulting in a diminished learning potential on tasks that could be verbally mediated. This was the first study that put forward that for certain procedural tasks other cognitive processes, such as verbal memory, are of critical importance during the process of acquisition. In later studies, variations of this explanation for protracted procedural learning in KS have also been put forward to explain task performance on the Tower tasks (Butters et al. 1985; Beaunieux et al. 2006). For example, following Beaunieux et al. (2006) deficits in declarative memory and executive functioning could explain the hampered learning performance in KS in the initial phase of procedural learning. This observation was striking because the patient population diagnosed with KS presents itself with a relatively heterogeneous range of cognitive symptoms (Jacobson and Lishman 1987). More specifically, deficits regarding executive functioning, such as interference of information and perseverative responses are commonly but not necessarily present in KS, thereby contributing differentially to the procedural memory difficulties (see Brion et al. 2014 for a review). Variable executive deficits in KS could therefore results in diminished learning performance for KS patients as a group, but result in preserved learning in individual cases without the executive deficits.

A different explanation to clarify diminished learning potential in KS for some procedural tasks, is the amount of cueing that is given by the task. This explanation was first put forward to explain the difference in learning performance between successful learning in the serial reaction time task, but less successful learning in the maze task (Nissen et al. 1989). The authors suggested that procedural learning in KS is dependent on the extent to which the stimulus information constrains the response selection (i.e., a maze task gives no cues indicating which response should be made, until a response has been attempted, while the serial reaction time task constantly gives cues how to respond). Cueing is specifically relevant for procedural learning in KS, since patients with KS frequently show marked executive deficits (Oscar-Berman 2012). Task performance on a maze task, but also a relatively complex task as the Tower task is highly dependent on executive functioning. By cueing such tasks, for example through errorless learning, it is possible to maximally bypass executive functioning to learn the procedure correctly. A third explanation to clarify the discrepancy between successful and impaired learning of procedural tasks in KS is the amount of feedback that is given by the task. Swinnen et al. (2005) showed that patients with KS had a better learning potential when feedback was given on their performance in a task in which they needed to make an arm movement. Here, perceptual information was made available to drive the motoric action (Swinnen et al. 2005). To summarize, a combination of cognitive preconditions that have not been met by the patients with KS and task-dependent aspects such as a lack of constraints and feedback during the task all can hamper procedural learning in KS.

New routes for using memory rehabilitation techniques to facilitate procedural learning in Korsakoff's syndrome

In the clinical literature, there has been a clear distinction between compensation and remediation of memory in memory rehabilitation. According to Rees et al. (2007), compensatory techniques, such as external or internal memory aids, for deficient memory functioning in patients with traumatic brain injury are currently the most promising forms of memory rehabilitation. Recent studies also show that remediation-based forms of therapy have the potency to increase memory functioning in patients with memory problems (Spreij et al. 2014). Unfortunately, many memory rehabilitation techniques have only been tested in patients with mild to moderate memory problems and not in patients with severe memory problems such as KS patients (see for example Cicerone et al. 2011). Moreover, it is currently unknown whether KS patients with extensive executive problems could successfully adopt memory aids to support their memory. In future research it would therefore be relevant to study the effects of compensatory techniques that decrease the amount of verbal mediation and increase the amount of cueing during a procedural task to support procedural learning. It would be relevant to specifically investigate the effectiveness of such techniques in groups of KS patients with mild and severe executive deficits separately. Recently developed technologies that could actively do so, also referred to as "smart objects" have not been adopted as memory rehabilitation aids in KS, while this could lead to amelioration of procedural learning based on other severe cognitive disorders (Stip and Rialle 2005). However, forms of memory rehabilitation that have been tested in patients with severe memory problems appear to be less successful compared to patients with less severe forms of amnesia (see for example Clare and Jones 2008).

Current state-of-the-art literature on memory rehabilitation in KS is solely based on uncontrolled case studies or small scale group studies (see Tables 4 and 5) and therefore warrants a rapid development of clinically relevant rehabilitation programs for KS. By formulating goals on forehand and restricting the learning procedure, the influence of deficits in declarative memory and executive functioning on procedural learning in KS can be reduced. Examples of such increased learning potential have been shown as the Tower of Hanoi task with three instead of four discs (Beaunieux et al. 1998), the maze task with blocked alleys (Nissen et al. 1989), and the successful introduction of prospective memory support devices (de Joode et al. 2013). Therefore, we suggest that a restriction of the formulated goals is recommended to facilitate procedural learning in KS. More recently, errorless learning has become increasingly popular as a teaching technique to guide successful procedural learning in multiple forms of severe cognitive problems, such as KS (Komatsu et al. 2000). In KS, errorless learning is more effective in learning face-name relationships and instrumental activities than learning with errors (Komatsu et al. 2000; Oudman et al. 2013). Recent findings suggest that procedural skills that are acquired through errorless learning are maintained over long periods and are relatively rapidly learned (Oudman et al. 2013). More research into the effectiveness of errorless learning for KS is of relevance, since the initial results of this type of interventions are promising.

Conclusion

The aim of the present review was to give an overview of procedural learning and memory in KS to disentangle what processes are preserved. Also, we wanted to highlight current advances in assistive technology and memory rehabilitation to support procedural memory and learning in KS. The currently available evidence suggests that patients with KS are able to learn procedures, although the extent of learning is highly task dependent. The learning potential in KS can be ameliorated by recent advances in memory rehabilitation, but the state-of-the art interventions have only been investigated in small patient groups with heterogeneous cognitive and intellectual functioning. Patients with KS show maximum procedural learning potential when the task is minimally dependent on other cognitive domains than procedural learning, when feedback is given during the task and when the task itself is restricted in response options. We conclude that when memory rehabilitation is adjusted to the specific needs of KS patients, this will increase their ability to learn procedures and their normally compromised autonomy is enhanced.

Chapter 9

Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: a comparison of trial and error and errorless learning.

Published as:
Oudman E., Nijboer T.C.W., Postma A., Wijnia J.W., Kerklaan S., Lindsen K., & Van der Stigchel S. (2013). Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: A comparison of trial and error and errorless learning. *Neuropsychological Rehabilitation, 23, 888-913. DOI:* 10.1080/09602011.2013.835738

Author Contributions: All contributing authors designed the research and wrote the paper, E.O., T.N., A.P., J.W., S.v.d.S. planned the data analysis, E.O., S.K., and K.L. conducted the experiment, E.O. performed the data analysis.

Abstract

Patients with Korsakoff's syndrome show devastating amnesia and executive deficits. Consequently, the ability to perform instrumental activities such as making coffee is frequently diminished in Korsakoff's syndrome. It is currently unknown whether patients with Korsakoff's syndrome are able to (re)learn instrumental activities. A good candidate for an effective teaching technique in Korsakoff's syndrome is errorless learning as it is based on intact implicit memory functioning. Therefore, the aim of the current study was two-fold: to investigate whether patients with Korsakoff's syndrome are able to (re)learn instrumental activities and to compare the effectiveness of errorless learning with trial and error learning in the acquisition and maintenance of an instrumental activity, namely using a washing machine to do the laundry. Whereas initial learning performance in the errorless learning condition was superior, both intervention techniques resulted in similar improvement over eight learning sessions. Moreover, performance in a different spatial layout showed a comparable improvement. Notably, in follow-up sessions starting after four weeks without practice, performance was still elevated in the errorless learning condition, but not in the trial and error condition. The current study demonstrates that (re)learning and maintenance of an instrumental activity is possible in patients with Korsakoff's syndrome.

Introduction

Korsakoff's syndrome is a brain disorder predominantly caused by alcoholism resulting in thiamine (vitamin B1) deficiency. Neurological damage in Korsakoff's syndrome is frequently found in the diencephalic and cerebellar structures. The disorder is characterized by severe anterograde amnesia for declarative knowledge (Kopelman, 1995; Sechi, & Serra, 2007). There is evidence that the most pronounced problems in Korsakoff's syndrome are found in remembering contextual information, such as spatial memory for exact locations of objects in space and relative object to location binding (Chalfonte, Verfaellie, Johnson, & Reiss, 1996; Kessels, Postma, Wester, & de Haan, 2000). Also, forming associations between temporal order information and spatial information is severely hampered (Postma, Van Asselen, Keuper, Wester, & Kessels, 2006). Besides problems with contextual memory, deficits in executive functions have also been reported in Korsakoff's syndrome (Van der Stigchel, Reichenbach, Wester, & Nijboer, 2012; Brand, Fujiwara, Borsutzky, Kalbe, Kessler, & Markowitsch, 2005; Jacobsen, Acker, & Lishman, 1990). The combination of memory and executive deficits has a massive impact on the patients' ability to carry out daily routines. In particular Korsakoff's syndrome patients are frequently reported to be unable to perform instrumental activities of daily living, such as making coffee or performing the laundry without assistance.

In the present study it was investigated whether Korsakoff's syndrome patients still have some potential for learning an instrumental activity of daily living, and if so which conditions would be most beneficial. Until now, this topic has received almost no consideration, although learning or relearning of potentially useful instrumental activities of daily living may increase the patient's functional autonomy (Kok, 1991, Wilson, 2008, Oudman, & Zwart, 2012). Moreover, investigations into application of intact memory in Korsakoff's syndrome in everyday situations might contribute to existing literature on memory processes in Korsakoff's syndrome. Most of the current literature on intact long term memory processes in Korsakoff's syndrome has been devoted to implicit memory. It is currently unresolved whether implicit memory is intact in Korsakoff's syndrome, although a variety of studies have suggested that implicit memory is relatively spared; more specifically implicit contextual learning (Oudman, Van der Stigchel, Wester, Kessels, & Postma, 2011), verbal repetition priming (Graf, Shimamura, & Squire, 1985), and perceptual priming (d'Ydewalle & Van Damme, 2007, Cermak, Verfaellie, Milberg, Letourneau, Blackford, & 1991, Fama, Pfefferbaum, & Sullivan, 2006) have been found to be intact. Nevertheless, motor sequence learning, conceptually- driven implicit memory and picture-fragment completion are relatively impaired compared to healthy control subjects (Van Tilborg, Kessels, Kruijt, Wester, & Hulstijn, 2012; Brunfaut & d'Ydewalle, 1996; Verfaellie, Gabrieli, Vaidya, Croce, & Reminger, 1996). A recent review suggested that implicit memory in Korsakoff's syndrome is restricted to operate in a rigid automatic fashion (Hayes, Fortier, Levine, Milberg, & McGlinchey, 2012). Korsakoff's syndrome patients may exhibit normal implicit memory performance on a variety of tasks, however when the task requires additional cognitive processes, such as executive functioning, task performance is impaired (Beaunieux, Pitel, Witkowski, Vabret, Viader, & Eustache, 2012).

A memory rehabilitation technique that has been shown to be effective in teaching new information and new procedures to individuals with severe memory impairment is errorless learning (Ehlhardt, Sohlberg, Kennedy, Coehlo, Turkstra, Ylvisaker et al., 2008; Kessels, & de Haan, 2000). Errorless learning is a teaching technique using feed-forward instructions, hereby preventing mistakes during the learning process. Feed-forward instructions (ie, how to perform a certain action) are given before actions to prevent learners from making mistakes. At each step the learner receives cues (see table 1 for an explanation of the procedure and examples of cues). In their now classical experiment, Wilson, Baddeley, & Evans (1994) reported five severely impaired amnesic patients with mixed etiology to successfully learn five tasks resembling everyday situations. For example, patients learned how to program an electronic aid. The authors argued that implicit memory is responsible for the consolidation of erroneous responses in errorful learning, whereas errorless learning helps implicit memory to overcome this failure in that only the correct response is strengthened. In particular, the literature associates the positive effects of errorless learning with a neuropsychological profile of significantly impaired explicit, conscious memory with relatively preserved implicit, unconscious memory (Evans, Wilson, Schuri, Andrade, Baddeley, Bruna, et al, 2000; Cohen, Ylvisaker, Hamilton, Kemp, & Claiman, 2010). Nevertheless, in some experiments on healthy (Kessels, Boekhorst, & Postma, 2005) and memory-impaired individuals (Hunkin, Squires, Parkin, & Tidy (1998) no relationship between the learned material and assessments of implicit memory became clear. Whether explicit memory is necessary for errorless learning has been the topic of an ongoing debate (see Clare, & Jones, 2008 and Li & Liu, 2012 for reviews). A possible explanation for the inconsistent results was provided by Page, Wilson, Shiel, Carter, & Norris (2006). The authors suggested that while both implicit and explicit memory (when functionally adequate) could contribute to learning in amnesia, implicit memory alone is sufficient to account for the observed errorless learning advantage. Nevertheless, this could be enhanced by explicit memory when sufficient residual explicit memory functioning is available. Support for the sufficiency of implicit memory was found in studies that showed that the severity of explicit memory problems increased the effectiveness of errorless learning in a group of severe amnesiacs (Klimkowicz-Mrowiec, Slowik, Krzywoszanski, Herzog-Krzywoszanska, & Szczudlik, 2008; Page et al., 2006).

The errorless learning technique might be beneficial for learning an instrumental activity. In fact, recent pilot trials and case studies suggest that errorless learning techniques may have positive effects on activities of daily living in dementia compared to learning techniques with errors (Thivierge, Simard, Jean, & Grandmaison, 2008; Clare, & Jones, 2008). For example, Dechamps et al., (2011) showed that errorless learning was an effective method to relearn instrumental activities of daily living in Alzheimer's dementia. Errorless learning was more effective than trial and error learning during a follow-up after one and three weeks, suggesting long-lasting beneficial effects for relearning instrumental activities of daily life with errorless learning. Thus far only few experimental studies have attempted errorless learning in Korsakoff's syndrome and their results are inconclusive with respect to the question whether errorless learning is beneficial compared to learning with errors. The errorless learning technique was successfully applied for learning fictitious face-name associations (Komatsu, Mimura, Kato, Wakamatsu, & Kishima, 2000). In this study, errorless learning was more effective than a learning condition with errors. However, Kessels and colleagues (2007) showed that both errorless learning and trial and error learning were equally effective methods to learn routes in Korsakoff's syndrome.

The main objective of the current study was to examine whether Korsakoff's syndrome patients still have some potential for learning an instrumental activity of daily living. Moreover, we wanted to investigate whether errorless learning could more effectively support the (re)learning and maintenance of an instrumental activity of daily living in Korsakoff's syndrome than trial and error learning. Based on earlier studies in dementia (e.g. Dechamps et al., 2011) and a meta-analysis on memory-impaired individuals (Kessels, & de Haan, 2000), we expected performance in the errorless learning condition to be superior to the trial and error condition. It would be relevant to rehabilitation of Korsakoff's syndrome patients to employ the most successful (re) learning and maintenance of an instrumental activity, since this would vitally increase the autonomy of Korsakoff's syndrome patients.

As a model for instrumental activities, we chose a laundry activity, since this is a complex but regular instrumental activity of daily living. To test whether the learning effect was long lasting, we included four follow-up sessions after four weeks without training or any form of practice, after eight regular learning sessions. Currently, little research has been devoted to generalizations of learned material without errors to a different context in patients with amnesia. The available evidence, however, indicates that new knowledge acquired using errorless learning is often inflexible and recall is best when there is a strong correspondence between contextual cues at recall with cues that were present when information was encoded (see Ptak, Van der Linden, & Schnider, 2010 for a review). Some generalizations follow from overlearning (Butters, Glisky, & Schachter, 1993). Moreover, some case studies suggest that full transference of a learned response is possible (Todd, & Barrow, 1998; Van der Linden, Meulemans, & Lorrain 1994). Therefore, the second objective of the current study was to investigate whether new knowledge that was acquired transfers to a different spatial context.

Methods

Participants

Thirty patients (mean age: 58.9 (SD=6.9); 28 males) with severe anterograde amnesia, diagnosed with Korsakoff's syndrome participated in this study. Eight patients were excluded from analysis to avoid a ceiling effect in the learning and follow-up sessions. Their initial performance was higher than 85% on the first learning session, suggesting that they were already able to perform the complex task at near optimal level prior to training. Hence no learning or follow-up effects could be established. Six Korsakoff's syndrome patients dropped out of the study during the learning or follow-up sessions; four because of motivational problems interfering with the testing procedure and two because of a medical condition that withheld the Korsakoff's syndrome patients from completing all sessions. The remaining 16 (8 errorless learning, 8 trial and error learning) patients completed all sessions. The patients were inpatients of the Korsakoff Centre 'Slingedael', Rotterdam, The Netherlands. All patients fulfilled the DSM-IV criteria for alcohol-induced persisting amnestic disorder (APA, 2000) and the criteria for Korsakoff's syndrome described by Kopelman (2002). The amnestic syndrome was confirmed by extensive neuropsychological testing. All patients were in the chronic, amnestic stage of the syndrome, none of the patients was in the confusional Wernicke psychosis at the moment of testing. For all patients, the current intelligence level of each participant had to be in concordance with the estimation of premorbid functioning based on occupational and educational history to exclude cases of dementia (Oslin, Atkinson, Smith, & Hendrie, 1998). Premorbid IQ was estimated with the Dutch Adult Reading Test (Schmand, Lindeboom, & van Harskamp, 1992), which is the Dutch version of the National Adult Reading Test (Christensen, Hazdi-Pavlovic, & Jacomb, 1991; McGurn et al., 2004). This score on this test is a predictor of premorbid intelligence of brain-damaged patients. General cognitive functioning was assessed with the Mini-Mental-State-Examination (MMSE; Folstein, Folstein, McHugh, 1975; Kok, Verhey, & Schmand, 2004). Only patients with estimated premorbid IQ scores higher than 80 and MMSE scores higher than 18 were included in the test protocol, to exclude patients with low intellectual or cognitive functioning interfering with the testing procedure, possibly caused by alcohol dementia (Kok, Verhey, & Schmand, 2004; Schmand, Lindeboom, & Van Harskamp, 1992). Moreover, all patients were younger than 70 years to minimize the possibility of senile dementia. All patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts. Other general exclusion criteria were presence of neurological disorders (head injury, stroke, epilepsy, etc.), illiteracy, and acute psychiatric conditions (psychosis, major depression, etc.), or physical conditions interfering with the testing procedure. The patients gave informed consent according to the standards of the Declaration of Helsinki.

Materials

A laundry task was selected since it requires multiple steps and is a commonly applied instrumental activity. Moreover, before this study took place, the laundry was performed by an external cleaning service. This minimized the chance that patients were already acquainted with the task prior to the procedure. The task was broken into small action sequences (see Table 1). The action sequences were transformed into verbal instruction. Motor sequences and explicit knowledge were scored using the same assessment procedure which was validated in a multidisciplinary team composed of a psychologist, an occupational therapists, a social worker and two members of the nursing staff.

Task

During a face-to-face interview with the patient, the aim of the project was explained in further detail, namely the (re)learning of a laundry activity. For all patients, the primarily responsible nurse was asked whether or not the patient was able to perform the laundry task. For all patients the nurse agreed that the patient was unable to perform the task and/or never performed the task during his/her stay in the clinic. Subsequently, the performance on the selected task was assessed. Half of the patients were instructed following the errorless learning condition, the other half of the patients were instructed following the trial and error condition. In the errorless learning condition, the therapist gave cues before the completion of the sequence according to the protocol as described in Table 1. The errorless learning method is described as a teaching technique that prevents people from making mistakes during learning. This contrasts with trial and error learning, in which guessing and errors are corrected after they have been performed. In the trial and error condition participants were allowed to make up three guesses (or a maximum duration of 20 seconds) before correction. Cues were only provided if the participant was unable to find and complete the next step correctly. The therapist prompted the patient to find a solution, using different questions related to the task. No errors were intentionally introduced in both conditions.

Primary Outcome Measures

The assessment procedure remained the same for all patients during all assessment sessions. The laundry activity was broken into action sequences (see Table 1). The assessment of each action step was made using 3 categories: (1) Deficit; (2) Questionable; and (3) Competent.

Deficit: this term designates the absence of answers or reactions. A patient who stopped and was not able to perform the task with additional repetitions of the verbal instructions was classified as having a deficit in this specific step (Score=1).

Questionable: this term refers to all actions from the patient that cannot be classified as correct (competent). A patient who showed hesitation and doubt in performing this step was classified as having a questionable performance in this specific step. This category involves: planning problems; the repetition of a step that has already been performed; verbal hesitation: asking questions such as "is it correct?". Motor hesitation such as touching the object and quickly retrieving the hand, and making small or aimless movements were also classified in this category (Score = 2).

Competent: the step is successfully performed without instructions (Score = 3).

After each step of the task sequence, the therapist filled in the assessment form for each step. For total score comparisons, the total scores per tasks were adjusted to a 100-point scale using the following formula: performance = (total score / 27) * 100. A performance of 100% therefore indicated perfect actions and planning (see Dechamps et al., 2011 for more details).

Table 1 - Description of the errorless learning and trial and error learning condition: the action sequence, verbalised by the therapist and examples of verbal cues

	Errorless learning	Trial and error learning
Technique	Errorless learning refers to the use of feed-forward instruction (ie, how to do) before actions to prevent learners from making mistakes.	Trial and error learning refers to the regular unstructured learning and is considered as control condition.
Guidance	At each step the patient receives verbal cues. Before the task is performed, the participant receives verbal instructions.	Guessing and errors are corrected after they have been performed by verbal instructions.
Instructions	"Here is the washing machine. I will ask you to perform your own the laundry on the 40 degrees express program". I will help you if you are unable to perform steps during the task".	
Error correction	The therapist allows the participant to find the solution (maximum of 5 seconds), if the answer or action is not immediately given, the participant receives a cue ("do the step"). If the participant is still unable to perform the task, additional verbal instructions are given. If no verbal instructions lead to the correct response, the step is performed by the therapist.	Erroneous responses are corrected by verbal cues after 2 trials or 20 seconds (approximately). The patient is encouraged to continue.
Action sequence	Examples of verbal cues	Examples of verbal cues
1. Bring the laundry basket to the washing machine	Cue: We take this basket.	Cue: We need to bring this basket, not this pile of clothes.
	Cue: We bring the basket to the laundry machine.	Cue: We need to bring the basket to the laundry machine.
2. Put the clothes in the washing machine	Cue: Put them in the machine.	Cue: This is not the correct machine, put them in the washing machine.
3. Close the door of the washing machine	Cue: Close the door.	Cue: First, close the door of the machine.
4. Open the soap box and put one spoon of soap in it	Cue: Open the box.	Cue: The machine is not ready to start yet, first put in the soap.
	Cue: Put a spoon of soap in the box	Cue: You should put a spoon of it in it.
5. Select the "40 degrees express" program on the program display by turning the switch	Cue: Select 40 express.	Cue: The Select 40 express program should be selected.
	Cue: Turn on the switch.	Cue: Turn on the switch

9

Table 1 - continued

	Errorless learning	Trial and error learning
6. Start the machine. After you pushed start we see each other in 30 minutes	Cue: Now start the machine.	Cue: You first need to start the machine.
7. Open the washing machine	Cue: Open the machine.	Cue: You first need to open the machine.
8. Put the clothes in the basket	Cue: Put the clothes in the basket.	Cue: Put the clothes in this basket
9. Hang the clothes on the laundry rack	Cue: Hang them on the rack.	Cue: The clothes should be hanged on the rack.

Week	1	2	3	4	5	6	7	8	9	10	11
Session	1 & 2	3 & 4	5 & 6	7 & 8					Follow-up 1 & 2	Follow-up 3 & 4	Spatial Follow-up

Figure 1. Time-frame of the experiment. Sessions were conducted twice a week, with a 4 week pause. Five follow-up sessions were conducted, four within the same spatial lay-out. The fifth follow-up session was in a different spatial lay-out.

Procedure

The therapists followed a two-day instruction on errorless learning at the care facility Krönnenzommer, Hellendoorn, the Netherlands before the start of the study. The training encompassed a course on the concept of errorless learning and training sessions on accurately rating the patients' performance. Moreover, the therapists followed two instruction sessions on differences between trial and error learning and errorless learning at the care facility Slingedael, Rotterdam, the Netherlands. For the task, patients with Korsakoff's syndrome were visited at their facilities eight times over a four-week period (twice a week) for a total of eight sessions. Five follow-up assessments (assessments occurred twice a week) (see Figure 1) were performed after four weeks without training. During the four weeks without training patients did not perform the laundry task. The laundry was performed by an internal laundry service. The goal of the first follow-up assessment was to investigate whether patients with Korsakoff's syndrome were still able to perform the instrumental activity. The goal of the second to the fourth follow-up was to examine whether patients were able to improve their performance on the instrumental activity. In the fifth follow-up assessment, the spatial layout of the procedure was changed such that patients performed the task in a washing room with a different spatial layout (see Figure 2). Only one follow-up assessment included a changed spatial layout to minimize the possible discomfort involved with performing the task in a different set-up. During each session, the participant learned the laundry task using the schedule that is presented in Table 1.

Figure 2. Left: The spatial layout of the eight learning sessions and four follow-up sessions. Right: the altered spatial layout for the session with a different spatial layout.

Assessment

All participants completed a short neuropsychological examination within one month prior to the start of the learning procedure. Patients were administered the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT; Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005) which measures immediate and long-term verbal memory. Verbal working memory capacity was assessed using the digit span of the Wechsler Adult Intelligence Scale (Uterwijk, 2000). Moreover, the Action Programme test of the Behavioral Assessment Dysexecutive Syndrome (BADS) was also conducted (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). In the Action Programme test participants are required to remove a cork from a small tube, making use of certain tools. This test shows adequate concurrent validity to assess executive functions, and assesses planning, problem solving and shifting (Norris, & Tate, 2000; Van Oort, Kessels, 2009). For all patients education level was assessed using seven categories, 1 being the lowest (less than primary school) and 7 being the highest (academic degree) (Verhage, 1964). These categories were converted to the internationally applied classification using years of education (Hochstenbach, Mulder, Van Limbeck, Donders & Schoonderwaldt, 1998).

Results

Demographic and neuropsychological characteristics

Demographic variables and neuropsychological test results of the patients are represented in Table 2. No statistically significant differences between the errorless learning and trial and error learning condition with respect to the demographic variables and neuropsychological test results of the Korsakoff's syndrome patients were found.

Table 2. Demographic variables and neuropsychological test results for the Korsakoff's patients

	errorless learning	trial and error learning	Statistic	*P*-value
Number of participants (m:f)	8 (8:0)	8 (8:0)		
Age (Mean, SD)	58.9 (6.9)	58.9 (7.2)	*t*(14)=0.76	.46
Years of Education (Mode, range) [a]	10.3 (8-19)	10.4 (6-19)	Mann-Whtney U=28.5	.72
MMSE (Mean, SD) [b]	23.0 (3.3)	22.5 (2.7)	*t*(14)=0.33	.74
IQ (Mean, SD)[c]	92.1 (8.7)	91.9 (12.4)	*t*(14)=0.05	.96
BADS Action Programme test (Mean, SD)[d]	2.4 (1.8)	2.8 (1.5)	*t*(14)=0.46	.65
WAIS III Digit Span Forward (Mean, SD)[e]	5.0 (0.5)	5.1 (1.1)	*t*(14)=0.28	.78
WAIS III Digit Span Backward (Mean, SD)[e]	3.4 (0.5)	3.8 (0.7)	*t*(14)=1.21	.25
Rey Auditory Verbal Learning total score 1-5 (Mean, SD)[f]	16.7 (4.5)	12.9(5.3)	*t*(14)=1.47	.17
Rey Auditory Verbal Learning free recall (Mean, SD)[f]	2.6 (6.2)	0.6 (0.9)	*t*(14)=0.90	.39
Rey Auditory Verbal Learning recognition (Mean, SD)[f]	18.5 (5.9)	20.0 (4.8)	*t*(14)=0.56	.58

MMSE = Mini-Mental State Examination; IQ = Intelligence Quotient; BADS = Behavioural Assessment Dysexecutive Syndrome; WAIS III = Wechsler Adult Intelligence Scale III;

[a] Years of Educations was scored using 7 categories: 1 = lowest (less than primary school), 7 = highest (university degree) (Verhage, 1964) and converted to the internationally applied classification (Hochstenbach et al., 1998)

[b] The standardised Dutch version of the Mini-Mental State Examination was assessed (Kok, Verhey, & Schmand, 2004).

[c] IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

[d] In the Action Programme test participants are required to remove a cork from a small tube, making use of certain tools. This test shows adequate concurrent validity to assess executive functions, and assesses planning, problem solving and shifting in Korsakoff's syndrome (Norris, & Tate, 2000; Van Oort, Kessels, 2009).

[e] Working memory span for the Wechsler Adult Intelligence Scale, raw scores (WAIS; Uterwijk, 2000).

[f] Raw score for the Dutch version of Reys Auditory Verbal Learning test. All patients scored within the first five percentiles for the total score 1-5 and free recall. (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005).

Laundry task

Figure 3 depicts the performance on the laundry task over time. Each data point reflects the performance on each assessment and was scored by a trained therapist.

Learning phase

Both groups performed equally well on the first learning session ($t(14) = 1.1$, $p=.291$), indicating no performance differences at the start of the protocol. To investigate whether errorless learning and trial and error learning techniques could effectively support the (re)learning of the laundry task in Korsakoff's syndrome, performance in eight consecutive learning sessions was examined for both conditions separately. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated for session in the errorless learning condition, but not for the trial and error condition.

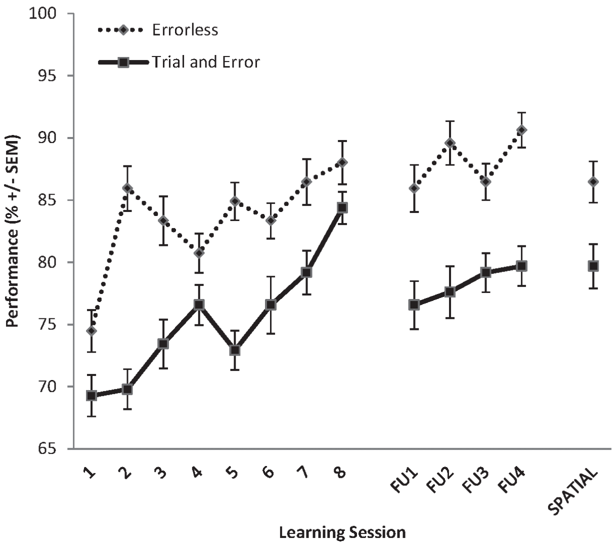


Figure 3. Performance on each learning session for Korsakoff's syndrome patients (n=16) in the errorless learning and trial and error Learning condition. For total score comparisons, the total scores per session were adjusted to a 100-point scale.

Therefore, we used Greenhouse–Geisser-corrected values for the results of the repeated measures ANOVA of this variable in the errorless learning condition. Importantly, a main effect for Session was found in the errorless learning condition ($F(4.755, 33.288) = 4.5$ MSE= 47.1, p=.003, $\eta_p^2 = .392$) and in the trial and error condition ($F(7,49) = 9.8$ MSE= 20.6, p<.0001 , $\eta_p^2 = .582$). The results suggest that during the learning phase both learning conditions improved. In order to inspect the benefits of the learning phase, performance on the first and the eighth session were compared in post-hoc 2 x 2 ANOVA on the first and last session of the learning phase. Prominently, a main effect for Session ($F(1,14) = 40.5$ MSE= 40,5, $p<.0001$, $\eta_p^2 = .743$) was found, indicating a learning effect over sessions. The Condition effect was not significant ($F(1,14) = 1.3$, $p=.281$, $\eta_p^2 = .083$), suggesting that performance was not statistically different between Errorless learning and Trial and Error learning. The interaction of Session X Condition was not significant $F(1,14) = 4.9$, MSE= 40,5, $p=.734$, $\eta_p^2 = .009$). For the Errorless learning condition an average improvement of 13.5% was found (SD=10.4%), while for the Trial and Error learning condition this was 15.1% (SD=7.4%). The results suggest that during the learning phase both learning conditions improved to an equal extent.

Based on visual inspection of the results (see Figure 3), it was expected that the errorless learning condition demonstrated an evident improvement in the second learning session compared to the first learning session. To investigate this expectation, the first and second session were compared in post-hoc repeated measures. The effect for Session was significant (first versus second) in the errorless learning condition ($F(1,7) = 12.6$ MSE = 41.5 $p=.009$ $\eta_p^2 = .644$), but not for the trial and error condition ($F(1,7) = 0.0$ MSE = 33.2 $p=.862$ $\eta_p^2 = .005$). Notably, for the errorless learning condition an average improvement of 11.5% was found (SD=9.1%), while for the trial and error condition this was 0.5% (SD=8.2%). Moreover, it was expected that in the errorless learning condition, learning flattened after the second learning session. To investigate this expectation, the second and eighth session were compared in post-hoc repeated measures. The effect for Session (second versus eighth) was not significant in the errorless learning condition ($F(1,7) = 1.4$ MSE = 12.4 $p=.275$ $\eta_p^2 = .167$), but was for the trial and error condition ($F(1,7) = 68.6$ MSE = 12.4 $p<.001$ $\eta_p^2 = .907$). The post-hoc analyses suggests that the performance in the errorless learning condition showed a significant increase in the second learning session, while this was not evident for the trial and error condition. After the second learning session, learning plateaud in the errorless learning condition, while it increased in the trial and error condition.

Without training

To inspect whether four weeks without any training or practice resulted in an inferior performance compared to the last learning session, the last learning session and the first follow-up session were compared for both conditions separately. Importantly, for the errorless learning condition, no significant effect for Session (eighth versus first follow-up) was found ($F(1,7) = .8$ $MSE = 22.3$ $p=.41$ $\eta_p^2 =.100$), indicating that four weeks without training or practice had no significant effect on task performance for the errorless learning condition. For the trial and error condition a negative trend was found ($F(1,7) = 5.1$ $MSE = 48.2$ $p=.059$ $\eta_p^2 =.42$), suggesting that four weeks without training or practice had a negative effect on task performance in the trial and error condition.

To examine whether four weeks without any training or practice resulted in a better performance compared to the first learning session, the first learning session and the first follow-up session were compared for both conditions separately. Importantly, for the errorless learning condition, a significant effect for Session (first versus first follow-up) was found ($F(1,7) = 6.9$ $MSE=76.3$ $p=0.03$ $\eta_p^2 = .50$), while no significant effect for Session (first versus first follow-up) was found in the trial and error condition ($F(1,7) = 3.3$ $MSE = 63.9$ $p=.11$ $\eta_p^2 = .32$). Compared to the first learning session, for the errorless learning condition an average improvement of 11.5% was found (SD=12.4%), while for the trial and error learning condition this was 7.3% (SD=11.3%). Together, the statistical analyses on the first follow-up session suggest that performance was still elevated in the errorless learning condition after four weeks without practice or training, without a significant decline in performance. In the trial and error condition performance was not significantly elevated compared to baseline.

Follow-up phase

To see whether four follow-up sessions would result in reinstatement of the initial learning effect in both learning conditions, performance in four follow-up sessions was examined for both conditions. Here the main effect of Session was not significant for the errorless learning condition ($F(3,21) = 1.9$ $MSE = 22.7$ $p=.165$ $\eta_p^2 =.211$) and the trial and error condition ($F(3,21) = .95$ $MSE = 17.2$ $p=.433$ $\eta_p^2 =.120$). The results suggest that both conditions did not show a significant improvement in the follow-up phase.

Spatial layout

To investigate whether the benefits of a learning technique would generalize to a different spatial context, the fifth follow-up session was compared to the last session with a different spatial context for both conditions. The Session effect was significant for the errorless learning condition ($F(1,7) = 7.0$ $MSE = 9.9$ $p=0.03$ $\eta_p^2 = .500$), but not significant for the trial and error condition ($F(1,7) = 0$ $MSE = 12.4$ $p=1$ $\eta_p^2 = .0$). This suggests that a different spatial layout has a negative impact on performance in the errorless learning condition, but not in the trial and error condition. To scrutinize whether the training program did have a positive impact on task performance in both learning conditions in a different spatial lay-out, the fifth follow-up session was compared to the first learning session. Here, the Session effect was significant for the errorless learning condition ($F(1,7) = 7.1$ $MSE =80.4$ $p=.032$ $\eta_p^2 =.505$) and the trial and error condition ($F(1,7) = 12.5$ $MSE =34.7$ $p=.010$ $\eta_p^2 =.641$), suggesting that both conditions did benefit from the training program. Compared to the first learning session, for the errorless learning condition an average improvement of 12.0% was found (SD=12.7%), while for the trial and error learning condition this was 10.4% (SD=8.3%). Together these results suggest that a different spatial layout did result in a lower task performance for the errorless learning condition, but not for the trial and error condition. However, task performance did show an improvement of 12.0% in the errorless condition and 10.4% in the Trial and error condition after the training program, which was a significant improvement for both learning conditions.

Correlations between test results

To further investigate the nature of instrumental learning, we performed additional correlations on the various neuropsychological test results and demographic variables. Correlations between neuropsychological test results and task performance in the first learning session are represented in Table 3. The correlations suggest that initial task performance showed a positive association with tasks intended to index encoding into long-term memory (Rey Auditory Verbal Learning Test, trial 1-5), executive planning skills (Behavioral Assessment Dysexecutive Syndrome Action Programme Test), and general cognitive functioning (Mini-Mental State Examination). Initial task performance demonstrated a negative correlation with a task intended to index working memory (Wechsler Adult Intelligence Scale - digit span backward). Moreover, initial task performance showed a negative trend with a task intended to assess speed of processing (Wechsler Adult Intelligence Scale - digit span forward), and a positive trend with a task intended to assess recognition of verbal material (Rey Auditory

Verbal Learning Test, recognition). Task performance in the first learning session did not significantly correlate with any other reported neuropsychological test scores or demographic variables in Table 3 (ps >.52). The results suggest that the performance of an activity of daily living (e.g. a washing activity) requires a complex set of cognitive functions rather than a single cognitive function. Implications of this finding are elaborated in the discussion.

Table 3. Pearson's correlations between the demographic variables, neuropsychological test results and task performance in the first learning session, learning in the learning phase, learning in the follow-up and learning in a different spatial layout (n=16).

	Peformance first learning session [a]	Learning in the learning phase [b]	Learning in the follow-up phase [c]	Learning in a different spatial layout [d]
Age (r, p-value)	-.18, p=.52	.26, p=.34	-.01, p=.99	.24, p=.38
Years of Education (r, p-value)	.07, p=.81	-.13, p=.64	-.08, p=.76	.11, p=.69
MMSE (r, p-value)	.52, p=.04	-.45, p=.08	-.35, p=.19	-.20, p=.45
IQ (r, p-value)	.06, p=.83	-.07, p=.80	-.04, p=.89	.07, p=.80
BADS Action Programme test (r, p-value)	.71, p=.00	-.46, p=.07	-.36, p=.17	-.36, p=.18
WAIS III Digit Span Forward (r, p-value)	-.45, p=.08	.06, p=.83	.05, p=.86	.10, p=.70
WAIS III Digit Span Backward (r, p-value)	-.57, p=.02	.00, p=.99	.14, p=.60	.16, p=.55
Rey Auditory Verbal Learning total score 1-5 (r, p-value)	.56, p=.04	-.59, p=.03	-.40, p=.15	-.48, p=.08
Rey Auditory Verbal Learning free recall (r, p-value)	-.06, p=.84	-.50, p=.05	-.13, p=.64	-.07, p=.79
Rey Auditory Verbal Learning recognition (r, p-value)	.46, p=.08	-.09, p=.74	.08, p=.78	.09, p=.75

For total score comparisons, the total scores per tasks were adjusted to a 100-point scale using the following formula: performance = (total score / 27) * 100. MMSE = Mini-Mental State Examination; IQ = Intelligence Quotient; BADS = Behavioural Assessment Dysexecutive Syndrome; WAIS III = Wechsler Adult Intelligence Scale III; RAVLT = Reys Auditory Verbal Learning Test.
[a] Task performance in the first learning session
[b] Learning in the learning phase was assessed by subtracting the performance score for the first learning session from the performance score in the eighth learning session.
[c] Learning in the follow-up phase was assessed by subtracting the performance score for the first learning session from the performance score in the first follow-up session.
[d] Learning in a different spatial layout was assessed by subtracting the performance score for the first learning session from the performance score in a different spatial layout.

To further investigate the nature of the learning effect in the learning phase, we performed additional correlations on the various neuropsychological test results (see Table 3) and the learning effect in the learning phase. Task learning in the learning phase was defined as the difference between task performance in the eighth learning session and the first learning session. The correlations suggest that task learning did show a negative association with a tasks intended to index encoding into verbal long-term memory (Rey Auditory Verbal Learning Test, trial 1-5). Moreover, a negative trend was found between task learning and a task intended to index verbal long-term memory (Rey Auditory Verbal Learning Test, free recall) and executive planning skills (Behavioral Assessment Dysexecutive Syndrome Action Programme Test). Task learning did not significantly correlate with any other reported neuropsychological test scores or demographic variables in Table 3 (ps >.08). The correlations suggest that the effectiveness of the teaching methods relates to tasks intended to index long-term memory and executive planning skills (Behavioral Assessment Dysexecutive Syndrome Action Programme Test). The implications of this pattern of results are discussed in the discussion.

As described, we observed that four weeks without any training or practice still resulted in better performance than in the first learning session. The difference between the performance score on the first session and the first follow-up session did not correlate with any of the reported neuropsychological test scores or demographic variables in Table 3 (ps >.17). Moreover, the difference between the performance score on the first session and the session with a different spatial layout did show a negative trend with a task indented to assess verbal long-term memory (Rey Auditory Verbal Learning Test, free recall). The difference between the performance score on the first session and the session with a different spatial layout did not correlate significantly with any of the reported neuropsychological test scores or demographic variables in Table 3. It has to be noted that the relatively small sample size is likely to contribute to the lack of significant correlations.

Discussion

The aim of this study was two-fold: to investigate whether patients with Korsakoff's syndrome are able to (re)learn instrumental activities and to compare the effectiveness of errorless learning with trial and error learning. Further, in order to examine whether (re)learning of an instrumental activity generalizes to a different context, we altered the spatial layout in the last phase of the study. The results of the present study clearly indicate that even severely amnesic patients can learn an instrumental activity in eight biweekly learning sessions. Interestingly, the errorless learning condition showed a sharp increase in task performance at the start of the learning sessions, while this was not evident for the trial and error condition. After the second trial, learning in the errorless learning condition plateau, while for the trial and error condition it increased. Moreover, after one month without any training or practice, performance was similar to the achievements on the final learning session for the errorless learning condition, but for the trial and error condition task performance had dropped again to baseline level. In the follow-up phase, consisting of four sessions, both conditions did not show improvements in task performance. Improvements generalized to a different context, namely a different spatial layout for both conditions. A change in spatial layout had a negative impact on task performance in the errorless learning condition, compared to task performance in the normal spatial layout, but task performance was still improved compared to baseline. Correlations suggested that initial task performance was positively associated with tasks intended to assess general cognitive functioning, verbal long-term memory and executive planning skills, but negatively with working memory. Instrumental learning, however, showed a negative association with a task intended to assess long-term memory and executive planning skills.

This is the first study to investigate whether an instrumental activity of daily living can be (re)learned by patients with Korsakoff's syndrome. The positive results of this study are promising for applying learning techniques in rehabilitation of Korsakoff's syndrome patients. This is particularly noteworthy as the loss of autonomy is characteristic for patients with Korsakoff's syndrome and (re)learning of instrumental activities might vitally contribute to the autonomy of the patients. Our results corroborate and extend previous studies that suggest that errorless learning can be successfully applied in Korsakoff's syndrome and other patients with memory problems (Kessels, & de Haan, 2000; Komatsu, Mimura, Kato, Wakamatsu, & Kishima, 2000; Kessels, Boekhorst, & Postma, 2005). Moreover, the results indicate a parallel to recent research on IADL learning in patients with dementia by means of errorless learning (Dechamps et al, 2011). It seems to be possible to obtain reliable improvements on task performance in both dementia and Korsakoff's syndrome. Importantly, also in dementia, superior performance for errorless learning became evident in a follow-up after weeks without training. A favorable task performance after a prolonged period of time in both studies suggests that errorless learning results in better consolidation of the learned material than trial and error learning. A possible explanation for the successful delayed recall of the learned material in errorless learning is that implicit memory contributes to the consolidation of the learned material. This explanation would be in line with Baddeley and Wilson's hypothesis (1994) which states that impaired explicit memory results in errors that interfere with learning and memory. If errors are eliminated, effective learning would result through the operation of relatively spared implicit memory. Furthermore, the results of superior performance for errorless learning in the follow-up are also compatible with the observations of Page et al., (2006). In their view, implicit memory for errors generated during trial and error learning leads to reduced performance since the implicit memory system does not distinguish between errors and correct responses. It has to be noted, however, that residual explicit memory could have a favorable effect on learning in both conditions in the current experiment, albeit the severity of the amnestic syndrome.

A major finding of the present study is that errorless learning yielded faster improvement at the start of the learning sessions than trial and error learning. As far as we know, the learning trajectory for (re)learning an instrumental activity has never been explicitly investigated in amnesiacs. Nevertheless, as supportive figures in earlier studies on errorless instrumental activity learning in dementia suggest, a fast errorless learning improvement compared to a slower improvement with errors is in line with earlier results (Lekeu, Wojtasik, Van der Linden, Salmon, 2002; Dechamps et al., 2011). It has to be noted that the instrumental task in the current experiment, but also in the aforementioned experiments in dementia, are unambiguous to perform for healthy subjects. In fact, a fast task improvement on instrumental tasks would be typical for healthy subjects. Nevertheless, amnesiacs and patients with dementia are severely hampered in the detection and correction of errors (Evans et al., 2000; Klimkowicz-Mrowiec et al., 2008). Therefore, a slower increase in performance for a condition with errors compared to a condition without errors could be explained by diminished cognitive functions (Rodriguez-Fornells, Kofidis, & Munte, 2004).

In the current experiment it was found that performance showed a plateau phase for the errorless learning condition after the second learning session, while it increased for the trial and error condition. A statistical explanation for the apparent plateau in performance is that performance was essentially quite high in the second learning session and showing a regression toward the mean after the second learning session. Based on earlier research in instrumental learning in dementia showing a comparable plateau in the errorless learning condition compared to the trial and error condition (Dechamps et al., 2011) it could also be argued that a plateau phase is an essential aspect of instrumental learning through errorless learning. This plateau could possibly reflect the transition of learning to maintenance of the instrumental task.

One of the remarkable findings of the current study is that performance levels were maintained to some extent even after a change in spatial layout for both learning conditions. A possible explanation for the current finding is that the generalization in our experiment was task specific. Although the spatial layout was changed, the required steps to perform the task were not changed. Task specific generalizations have been found in studies on different forms of amnesia (Schmidt, 2000; Berg, Koning-Haanstra, & Deelman, 1991), but have not been described for the spatial domain in Korsakoff's syndrome. It is commonly assumed that a full correspondence between the situation at encoding and recall is necessary to obtain robust improvements in errorless learning paradigms (Thöne, 1996; Kessels & de Haan, 2000; Ptak, Van der Linden, & Schnider, 2010). To our knowledge the importance of correspondence between encoding and recall was not discussed for trial and error learning specifically. In the current experiment, we found a small but significant decline in performance for the errorless learning condition in a different spatial layout suggesting that in memory rehabilitation for Korsakoff's syndrome through errorless learning the correspondence between the encoding and test situation should be maximized. It has to be acknowledged that even though the generalization manipulation in the current experiment was fairly limited in nature and extent, the current findings as such open a new perspective on transference of learning to a different spatial layout.

Since there is a large discrepancy between performing an instrumental task or a neuropsychological test, correlational analysis between task performance and cognitive tests are difficult to interpret in the current experiment. Nevertheless, we found that initial task performance was positively correlated with neuropsychological tasks intended to assess general cognitive functioning, verbal long-term memory and executive planning skills, but negatively with a task intended to assess working memory. These results suggest that a combination of cognitive skills are required to perform an instrumental activity of daily living, instead of a single cognitive function. Recent studies by Beaunieux et al., (2012) and Swinnen, Puttemans, & Lamote (2005) also suggested that long term memory, working memory, and executive functioning are related to the performance on a procedural task in Korsakoff's syndrome. To our knowledge, a negative correlation between procedural performance and working memory was not found in earlier research. This result should be interpreted with caution, since the sample sizes are relatively small and a large number of correlations are examined. A possible explanation for this finding, however, is the relatively small variation in scores on the working memory task in the current Korsakoff's syndrome sample.

In the correlational analysis examining the severity of memory and executive impairment and gain from both learning techniques, long-term memory and executive functioning were negatively correlated to the acquisition of the instrumental activity. This finding suggests that the more severely impaired patients did gain greater benefit from the learning techniques than less severely impaired patients. A possible explanation for this finding is that long-term memory and executive functioning, two cognitive domains that are essentially restrained in Korsakoff's syndrome (Van der Stigchel, Reichenbach, Wester, & Nijboer, 2012), negatively affect learning mechanisms in learning an instrumental activity of daily living. This finding is in line with an earlier study by Klimkowicz-Mrowiec and colleagues (2008) suggesting that patients with more severe amnesia due to Alzheimer's dementia outperformed patients with less severe amnesia on a task intended to assess procedural learning. Also, Evans and colleagues (2000) found a comparable negative relationship between a task intended to assess daily memory (RBMT) and learning names, specifically for the errorless learning condition in patients with acquired memory deficits. To our knowledge, relationships between executive functioning and memory rehabilitation through errorless learning have not been the scope of recent literature. Recent attempts to employ errorless learning as a rehabilitation technique for aphasia suggest that executive functions do have an influence on successful rehabilitation (Fillingham, Sage, & Ralph, 2005).

Importantly, not only memory functioning seems to have an impact on the effectiveness of teaching techniques in Korsakoff's syndrome in our study. As the negative relationship between a neuropsychological task intended to assess executive functioning indicates executive functioning is also relevant to the effectiveness of a teaching technique.

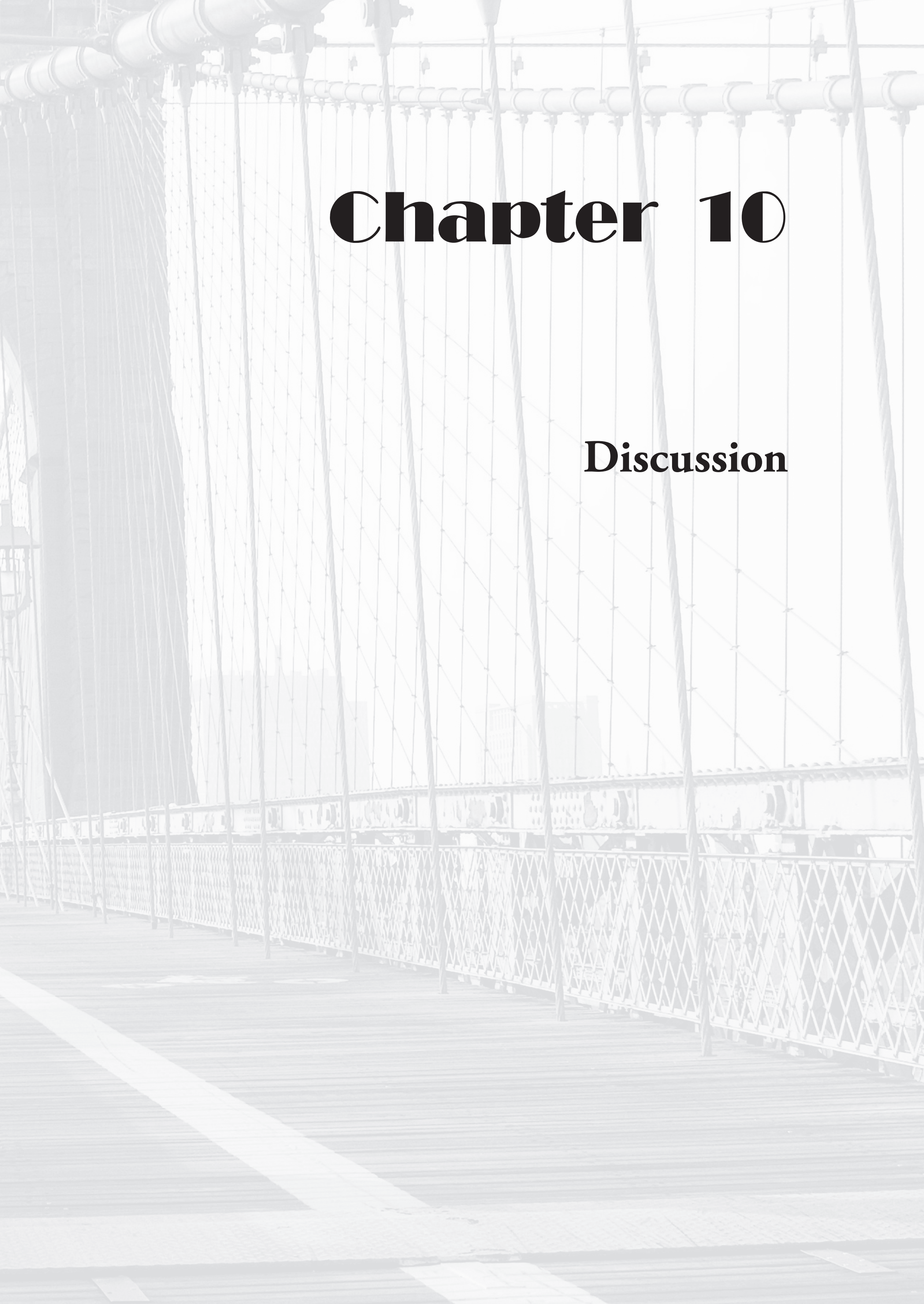
It should be noted that both the errorless learning condition and the trial and error condition did not show a significant task improvement in the follow-up phase, although this could be expected as the task is repeated in the follow-up sessions. An explanation for this finding is a ceiling effect in the follow up phase. The average performance in the first follow-up session was already quite high (81.3%), suggesting a near to perfect task performance.

There are also some methodological considerations that have to be taken into account in the interpretation of the present findings. Although 30 Korsakoff's syndrome patients were initially included in the experiment, results of only 16 patients were considered for data analysis. This has negative implications for the statistical power of the current experiment. Nevertheless, no statistically significant differences between the errorless learning and trial and error learning condition with respect to the demographic variables and neuropsychological test results of the Korsakoff's syndrome patients were found. Moreover, we would like to stress that in a recent review on procedural learning in Korsakoff's syndrome, only a small minority of studies included more than 10 Korsakoff's syndrome patients (Hayes et al., 2012). We suggest that our results require replication in larger samples of Korsakoff's syndrome patients.

Although all of our patients were severely hampered on long-term memory and diagnosed with Korsakoff's syndrome after neuropsychological testing and multidisciplinary diagnostics (Table 1), not all patients initially showed impaired task abilities on the first learning session of the laundry activity. A methodological concern is the exclusion of eight participants, because they were already able to perform the laundry. Before the experiment took place, we tried to control for this by asking the primary responsible nurse whether a patient was able to perform or did perform the laundry during the stay at the clinic. Apparently, a number of participants did not perform the laundry before the experiment, but were able to perform the laundry when asked. The exclusion of participants could suggest that both learning methods in our study are only successful for Korsakoff's syndrome patients that are unable to perform the instrumental task in our experiment, but are not successful for more complicated instrumental tasks. This would require further investigations in a group of high-functioning Korsakoff's syndrome patients.

In the current study the trial and error learning condition did benefit from the training program in the learning phase. We suggest that both implicit and explicit memory could have contributed to successful trial and error learning in the current study. An important finding by Kessels, van Loon, & Wester, (2007) was that trial and error learning was effective for route learning in Korsakoff's syndrome although patients had no explicit knowledge of prior sessions, suggesting that implicit memory could also be involved in trial and error learning. In the current study, however, there is the possibility that residual explicit memory did contribute to trial and error learning since the trial and error learning condition did score higher than zero on neuropsychological tasks intended to assess long-term memory (see table 2). The neurocognitive basis of trial and error learning warrants future investigation.

In conclusion, the results of the present study indicate that Korsakoff's syndrome patients could (re)learn and maintain an instrumental activity by means of errorless learning and trial and error learning. Errorless learning was, however, more effective for maintaining the instrumental task. Improvements generalized to a different context, namely a different spatial layout. The current study suggests that despite the severity and chronicity of the amnesia, patients with Korsakoff's syndrome have a residual memory potential to learn and maintain instrumental activities of daily living.



Chapter 10

Discussion

The focus of this thesis was twofold: to improve the diagnosis of Wernicke Encephalopathy (WE) and Korsakoff'ssyndrome (KS) and to gain a better understanding of memory, learning and rehabilitation in KS. In the first part of this thesis, the diagnosis of KS and WE was explored to increase the knowledge on how clinicians could diagnose this multiphase syndrome and assess the needs of patients that have been diagnosed with KS. In the second part of this thesis, novel findings on explicit memory problems and residual memory in KS were discussed to elucidate the complexity of the human memory system. In the third part of this thesis, memory rehabilitation of KS patients was central, aiming to increase the clinical implications of learning potential in KS. This discussion starts with an overview and discussion of the main findings of our studies per section. Subsequently, we conclude how these findings contribute to a better understanding of diagnosis, memory and rehabilitation in KS and make recommendations for future research and advances in clinical care.

Section 1 - Diagnosis of Wernicke's Encephalopathy and Korsakoff's syndrome

WE is a life-threatening, acute neuropsychiatric emergency caused by vitamine B1 (thiamine) deficiency. In western society this deficiency is usually caused by chronic alcoholism and self-neglect, but there are other causes of WE such as starvation, persistant vomiting, chronic infections of the intestines, post-partum illness, and various forms of cancer (Sechi & Serra, 2007). Untreated WE leads to death in up to 20% of the cases (Harper et al., 1986). Although it has been known for over 60 years that treatment with high doses of parenteral (intravenous or intramuscular) thiamine replacement therapy has the potency to improve the neuropsychiatric syndrome in WE, this is still uncommon practice (de Wardener et al., 1947; Isenberg-Grzeda et al., 2012; Thomson et al., 2013). Therefore, the majority of patients (68%) develop KS after weeks or months of WE (Day et al., 2008). In chapter 2 of this thesis a case study was presented of a female patient with a history of alcohol abuse that did survive WE, but did not receive appropriate treatment with thiamine replacement therapy. In fact, she was left untreated for more than five days. A broad pattern of cognitive and neuropsychiatric problems became apparent after four and sixteen months following admission to the hospital. At both times her behavior was characterized by incoherence, attentional deficiency and confusion. The patient showed a distinctive pattern of impairments that resembled the acute symptoms of WE, suggesting that WE can become chronic when untreated. A prime reason to report this case study was to stress the importance to have a high index of suspicion of WE in confused alcoholics. This case study also highlights the importance of active parenteral thiamine replacement therapy to prevent the development of chronic brain damage. In some countries malnourishment in alcoholics has received political attention leading to measures such as thiamine enrichment of bread flour. This form of preventive medicine has had astounishing consequences on the prevalence rates of WE in Australia, as shown by Harper and colleagues (1998). In their brain autopsy findings, a more than fourfold decrease of WE cases was visible before and after this enrichment (4.7% to 1.1% of the autopsy cases).

In chapter 3 a different diagnostic issue was raised. To diagnose KS with certainty, comprehensive cognitive testing is necessary. However, cognitive testing is time consuming, requires skilled clinicians, and is demanding for the patient. Therefore cognitive screening instruments such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) have been developed to provide an impression of cognitive problems in a short time span. Although the MMSE has been widely applied in neurological and psychiatric patients in a variety of settings, there were no studies available on the usability of the MMSE in KS. Moreover, it was unknown whether the more recently developed MoCA could better detect the cognitive problems in KS, although its capability to detect KS with high certainty was already clear (Wester, Westhoff, Kessels, Egger, 2013). The aim of the study in chapter 3 was to examine the psychometric properties and diagnostic validity of both cognitive screening instruments in KS patients. A representative sample of 30 patients with KS and 30 age-, education-, gender- and premorbid-IQ-matched controls was administered the MoCA and MMSE. The results showed that both cognitive screening instruments have adequate psychometric properties for the detection of KS, but the MoCA is superior to the MMSE for this specific patient population. This study shows that cognitive screening instruments that have originally been developed to detect dementia are also applicable to a population of alcoholics with suspicion for KS. Moreover, the MoCA is better able to detect KS than the MMSE and is therefore the cognitive screening instrument of choice to detect KS.

In the last chapter of this section, Quality of life (Qol) in patients with KS in a long-term care facility is discussed in comparison to that in dementia patients under similar housing conditions. Qol is used as a term for general well-being of individuals.

Assessments of Qol are frequently performed to diagnose the needs of patients in long-term care facilities. In this chapter the QUALIDEM, a proxy-based measure of Qol was administered. The nursing staff was instructed to score the 37-item observational scale for 72 patients with KS and 75 patients with dementia. The results of this cross-sectional study showed that the Qol in patients with KS in long-term care was very different from elderly patients with dementia even after correction for age and facility. Patients with KS tended to have more social relationships, positive emotions and less restless behavior than patients with dementia, but felt less at home in a long-term care facility. An important conclusion therefore seems that patients with KS are in need of specialized long-term care facilities and care programs to accomplish their specific needs. This study forms an initial starting point into the elucidation of Qol in KS, but there are still many methodological issues that need to be resolved. A central issue for this field of research is how self-report of patients with KS could contribute to the impression of their well-being, despite the severity of their cognitive problems and lack of illness insight.

Section 2 – Spared and impaired memory capacities in patients with Korsakoff's syndrome

Severe explicit memory loss has been described as a central symptom of KS (see for example Kopelman et al., 2009 and Kessels & Kopelman, 2012). Although the amnesia in KS patients affects all subdomains of explicit memory, there is considerable evidence that KS patients have the most pronounced problems in remembering contextual information (Chalfonte et al., 1996; Kessels et al., 2000; Postma et al., 2006). Following the context-memory deficit hypothesis the facets of the memory for the moment and place that an event occurs are disproportionally disturbed in KS, compared to the memory itself (Mayes et al., 1991). One of the most important contextual features, spatial information, is clearly affected in KS. This impairment includes memory for exact spatial information as well as relative object-to-location binding (Kessels et al., 2000). Moreover, patients with KS show pronounced problems in forming associations between temporal order information and spatial information (Postma et al., 2006). Although severe memory problems in general and contextual memory problems in specific are essential characteristics of KS, not all memory components seem to be impaired to the same extent. For example, there is ample evidence for succesfull repetition priming in KS (Cermak et al., 1991; d'Ydewalle

& van Damme, 2007) or motor sequence learning (Nissen et al., 1989), suggesting that forms of implicit memory are relatively better preserved than explicit memory. Multiple aspects of residual memory and learning potential are discussed in the second section of this thesis.

In chapter 5 working memory and long-term memory in KS were compared based on the type of information, namely verbal and spatial information. The aim of the study was to investigate whether patients with KS have stronger verbal or spatial memory difficulties and whether these memory difficulties were most apparent in the working memory phase, the long-term memory encoding phase or the long-term memory retrieval phase. The results showed that patients have better performance on indices of spatial memory then verbal equivalents of this task. Moreover, task performance was better in the working-memory phase than in the long-term learning phase, suggesting that working memory is better preserved in KS. It is possible that residual nondeclarative memory supported this spatial learning effect. Based on the findings of this chapter it is of relevance to include indices of spatial memory in regular neuropsychological examinations.

Regarding residual memory and learning, there is still considerable debate whether patients with Korsakoff's syndrome are fully able to learn and maintain new information on an implicit level. The study presented in chapter 6 aimed to investigate whether patients with KS are capable to learn spatial regularities in the implicit contextual learning paradigm. In a typical implicit contextual learning paradigm, subjects need to find a target among a number of distractors during visual search. Some of the configurations of stimuli are repeated during the experiment resulting in faster responses than for novel configurations, without subjects being aware of their repetition. To check for awareness, the subjects are asked to indicate whether configurations were presented during the experiment in a control experiment. In this study, 18 patients with Korsakoff's syndrome and 22 age-, IQ- and education matched controls performed a typical implicit contextual learning paradigm and a paradigm intended to index spatial working memory. The patients were able to learn the spatial regularities without conscious awareness, but showed hampered task performance on the spatial working memory task. Stikingly, the task performance on the implicit contextual learning task was comparable in KS patients and healthy controls, suggesting that implicit contextual learning is spared in KS. Despite abundant evindence that spatial context memory is impaired in KS we now demonstrate residual implicit context processing. This fascinating dissociation between explicit contextual learning and implicit contextual learning in KS suggests that both memory capacities rely on separate neural circuits.

Spatial context is particularly relevant in navigation. In chapter 7 of this thesis, the aim was to assess to what extent KS patients can acquire spatial information during a spatial navigation task. Furthermore, we also examined whether residual spatial acquisition in KS is based on automatic or effortful coding processes. To do so, 20 patients with KS and 20 age- and IQ-matched controls performed six tasks on spatial navigation after navigating once through a residential area. Ten participants per group were instructed to pay close attention, while ten received mock instructions. The results showed that KS patients were hampered on almost all tasks that tested for navigational knowledge, but their performance was superior to chance level on a route time and distance estimation tasks, a map drawing task and a route walking task. Moreover, their distance estimations were preserved compared to healthy controls. For KS patients, performance was comparable in the group that received the instruction to pay close attention to the route and the group that received mock instructions, while this was not the case for healthy controls. The intention to learn was beneficial for the map drawing task and route walking task compared to the mock instructions in healthy control subjects, suggesting that both aspects of spatial navigation are not entirely automatically processed but require intentional learning. This result also suggests that patients with KS are still able to acquire spatial information during spatial navigation based on automatic coding processes, although their performance is vastly compromised compared to healthy controls. This finding is relevant for the rehabilitation of patients with KS in that it clearly indicates that patients might be able to learn aspects of spatial navigation despite their global amnesia.

Section 3 – Rehabilitation and treatment for patients with Korsakoff's syndrome

Due to the severity of the cognitive and neuropsychiatric problems, patients with KS are in need of specialised rehabilitation and chronic care facilities. Currently, little is known about the long term care of patients with KS and how they could be rehabilitated effectively. As described in section two there is still learning potential in patients with KS despite their severe memory problems. The studies presented in this thesis suggest that although memory difficulties in KS are most profound in declarative memory ("knowing what"), procedural learning ("knowing how") is better preserved in KS. In chapter 7 of this thesis, a review on procedural learning and the current advances in memory rehabilitation in KS is presented. The papers included in the review offer substantial evidence for residual procedural learning potential in KS, despite the large variety of studies that were reviewed over a time span of more than 45 years (1976-2013). On a majority of tasks, patients with KS are able to learn and maintain procedures, but in some tasks procedural learning does not reach optimal levels. In the available literature, suboptimal performance in KS is explained as caused by cognitive problems in other neurocognitive domains that hamper procedural learning, a lack of cuing during the task and a lack of feedback during the task. By formulating goals on forehand and restricting the learning procedure, the influence of deficits in declarative memory and executive functioning on procedural learning in KS can be reduced. Over the past decades, the knowledge how to apply memory aids in KS has increased to some extent, but the body of research on assistive technology is still in its infancy.

A particulary promising form of memory rehabilitation is errorless learning. Errorless learning is a teaching technique, using feed-forward instructions, that has been suggested to be based on implicit learning and memory. In chapter 9 the aim was two-fold: to investigate whether patients with Korsakoff's syndrome are able to (re)learn instrumental activities, and to compare the effectiveness of errorless learning with trial and error learning. Feed-forward instructions (i.e., how to perform a certain action) are given before actions to prevent learners from making mistakes. In this study, eight KS patients received errorless instructions, while eight KS patients received trial and error instructions to learn how to operate a washing machine to do the laundry. Both groups learned equally well over the first eight learning sessions, but after one month without training the patients in the errorless learning group showed better task performance than the patients in the trial and error group, suggesting that errorless learning is an effective teaching technique to support (re)learning of an instrumental activity and may lead in particular to long term advantages. In a different spatial lay-out, task performance was hampered in the errorless condition, suggesting that it is relevant to maximize the the correspondence between the encoding and test situation for (re)learning instrumental activities of daily living.

Conclusions

The focus of the thesis was twofold: to improve the diagnosis of Wernicke Encephalopathy (WE) and Korsakoff's syndrome (KS) and to gain a better understanding of memory, learning and rehabilitation in KS. Regarding the central diagnostic issues presented in the first section of this thesis, the main conclusion is that WE and KS are still quite unfamiliar neuropsychiatric disorders that require specific attention from clinicians that work with alcoholics. Clinicians should have a high suspicion for WE in alcoholics, and actively treat them with intravenuous or intramuscular thiamine replacement therapy. In the chronic phase of KS cognitive screening instruments that have been developed to detect dementia, such as the MoCA, can successfully be applied to support the detection of KS. After diagnosis of KS, patients are in need of specific care programs and facilities that are essentially different from regular dementia care, because of the specific needs of this patient group.

Regarding the second focus of this thesis presented in the second and third section, one particularly emergent finding is that patients with KS are clearly still able to learn, maintain and recall non-declarative or implicit information despite severe declarative or explicit amnesia. Residual memory and learning was found along the continuum of a controlled experimental design to everyday life. A specific instance of residual learning in KS was shown in the implicit learning of spatial regularaties from our surroundings. The findings in the second section of this thesis extend the context-memory deficit hypothesis by Mayes (1991) which states that all facets of memory for the moment and place that an event occurs are disproportionally disturbed in KS compared to the memory itself. The presented studies suggest that severely compromised explicit contextual learning is accompanied by spared implicit contextual learning. In the final section of this thesis it was shown that cognitive rehabilitation could increase the restricted autonomy of the KS patients. When intensive use of other cognitive functions becomes necessary in the required learning action, memory rehabilitation is compromised in KS. It is therefore needed to support the learning process in KS by means of memory aids, feedback during the required task and goal-restriction. The last section of this thesis shows that errorless learning could successfully be applied to learn patients with KS novel instrumental activities of daily living, hereby increasing the autonomy of the patients.

Recommendations

Although cognitive and neurological functioning in KS has received some attention in the literature, clinical aspects of patients with WE and KS have largely been neglected. Incidence and prevalence rates are outdated, quality of life is seldom reported, and the first reports on the general characteristics of the institutionalized patient group have only recently been described (Gerridzen & Goossensen, 2014). Contributive to this hiatus in the literature could be the relative rarity of the disease, the avoidance of care by the patients, but also the relatively small number of facilities that have specialized in KS. Current state-of-the-art treatment knowledge on KS is solely based on case studies or small scale group studies and warrants a rapid development of clinically relevant care and rehabilitation programs for KS. It is therefore essential to broaden the research area on KS substantially and increase the number of clinical studies for a better recognition of KS, and improved treatment perspectives for patients with KS. To enhance treatment programs for patients with KS, residual contextual learning and memory deserve considerable attention. As illustrated in this thesis, patients with KS can, to some extent, compensate their explicit memory difficulties by implicit learning. Residual learning potential is relevant to perform activities of daily living, by this means increasing autonomy and quality of life of these intriguing patients. If anything the research presented in this thesis forms an initial step in reconstructing cognition in KS.

References

Alterman, A.I., Kusher, H., & Holahan, J.M. (1990). Cognitive Functioning and treatment outcome in alcoholics. *Journal of Nervous and Mental Disease, 178,* 494-499. DOI: 10.1097/00005053-199017880-00004

Alves, L., Simões, M.R, Martins, C., Freitas, S., & Santana, I. (2013). Premorbid IQ influence on screening tests' scores in healthy patients and patients with cognitive impairment *Journal of Geriatric Psychiatry and Neurology, 26,* 117-126. DOI: 10.1177/0891988713484194

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders 4th ed., textual revision* Washington DC, United States of America: American Psychiatric Association.

Anderson, J.R. (1992). Automaticity and the ACT* theory. *American Journal of Psychology*, *105*, 165-180. DOI: 10.2307/1423026

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. H. Bower (Ed.), *The psychology of learning and motivation (Vol. 8)*. London: Academic.

Baddeley A.D., & Wilson B.A. (1994). When implicit learning fails: amnesia and the problem of error elimination. *Neuropsychologia*, *34*, 53-68. DOI:10.1016/0028-3932(94)90068-X

Baddeley, A.D. (2001). Is working memory still working? *American Psychologist, 56*, 851-864. DOI: 10.1037/0003-066X.56.11.851

Barnes, K.A., Howard Jr., J.H., Howard, D.V., Gilotty, L., Kenworthy, L., Gaillard, W.D., & Vaidya, C.J. (2008). Intact Implicit Learning of Spatial Context and Temporal Sequences in Childhood Autism Spectrum Disorder. *Neuropsychology, 22*, 563-570. DOI: 10.1037/0894-4105.22.5.563

Barnett, V., & Lewis, T. (1994). *Outliers in statistical data* (3rd ed.) Chichester: John Wiley & 345 Sons.

Beaunieux, H., Desgranges, B., Lalevée, C., de la Sayette, V., Lechevalier, B., & Eustache, F. (1998). Preservation of cognitive procedural memory in a case of Korsakoff's syndrome: methodological and theoretical insights. *Perceptual and Motor Skills*, *86*, 1267–1287. DOI: 10.2466/pms.1998.86.3c.1267

Beaunieux, H., Hubert, V., Witkowski, T., Pitel, A.L., Rossi, S., Danion, J.M., Desgranges, B., Eustache, F. (2006). Which processes are implicated in cognitive procedural learning? *Memory*, *14*, 521-539. DOI: 10.1080/09658210500477766

Beaunieux, H., Pitel, A.L., Witkowski, T., Vabret, F., Viader, F., & Eustache, F. (2013). Dynamics of the cognitive procedural learning in alcoholics with Korsakoff's syndrome. *Alcoholism, Clinical and Experimental Research, 37*, 1025–1032. DOI:10.1111/acer.12054

Berg, I.J., Koning - Haanstra, M., & Deelman, B.G. (1991). Long-term effects of memory rehabilitation: A controlled study. *Neuropsychological Rehabilitation, 1*, 97-111. DOI: 10.1080/09602019108401384

Blake, H., McKinney, M., Treece, K., Lee, E., & Lincoln, A.B. (2002). An evaluation of screening measures for cognitive impairment after stroke. *Age and Ageing, 31,* 451-456. DOI: 10.1093/ageing/31.6.451

Blansjaar, B.A., & van Dijk, J.G. (1992). Korsakoff minus Wernicke syndrome. *Alcohol and Alcoholism*, *27*, 435-437.

Blansjaar, B.A., Takens, H., Zwinderman, A.H. (1992). The course of alcohol amnestic disorder: A three-year follow-up study of clinical signs and social disabilities. *Acta Psychatrica Scandinavia*, *86*, 240–246. DOI: 10.1111/j.1600-0447.1992.tb03260.x

Bliwise, D.L., Carroll, J.S., Lee, K.A., Nekich, J.C., Dement, W.C. (1993). Sleep and "sundowning" in nursing home patients with dementia. *Psychiatry Research*, *48*, 277-292. DOI: 10.1016/0165-1781(93)90078-U

Bouman, A.I., Ettema, T.P., Wetzels, R.B., van Beek, A.P., de Lange, J., Dröes, R.M. (2011). Evaluation of Qualidem: a dementia-specific quality of life instrument for persons with dementia in residential settings; scalability and reliability of subscales in four Dutch field surveys. *International Journal of Geriatric Psychiatry*, *26*, 711-722. DOI: 10.1002/gps.2585

Brady, T.F. & Chun, M.M. (2007). Spatial constraints on learning in visual search: Modelling contextual cuing. *Journal of Experimental Psychology: Human Perception and Performance, 33,* 798-815. DOI: 10.1037/0096-1523.33.4.798

Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J., & Markowitsch, H.J. (2005). Decision-making deficits of Korsakoff patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology*, *19*, 267–277. DOI: 10.1037/0894-4105.19.3.267

Brion, M., Pitel, A.L., Beaunieux, H., & Maurage, P. (2014). Revisiting the Continuum Hypothesis: Toward an In-depth Exploration of Executive Functions in Korsakoff Syndrome. *Frontiers in Human Neuroscience*, *8*, 498. DOI: 10.3389/fnhum.2014.00498

Brooks, D.N., Baddeley, A.D. (1976). What can amnesic patients learn? *Neuropsychologia*, *14*, 111-122. DOI: 10.1016/0028-3932(76)90012-9

Brunfaut, E., & d'Ydewalle, G. (1996). A comparison of implicit memory tasks in Korsakoff and alcoholic patients. *Neuropsychologia*, *34*, 1143–1150. DOI: 10.1016.0028-3932(96)00032-2

Bucks, R.S., & Willison, J.R. (1997). Development and validation of the Location Learning Test (LLT): A test of visuo-spatial learning designed for use with older adults and in dementia. *Clinical Neuropsychologist,11*, 273-286. DOI: 10.1080/13854049708400456

Burney-Puckett, M. (1996). Sundown syndrome: etiology and management. *Journal of Psychosocial Nursing and Mental Health Services*, *34*, 40-43.

Butters, N., Wolfe, J., Martone, M., Granholm, E., Cermak, L.S. (1985). Memory disorders associated with Huntington's disease: Verbal recall, verbal recognition and procedural memory. *Neuropsychologia*, *23*, 729-743. DOI: 10.1016/0028-3932(85)90080-6

Butters, N., Wolfe, J., Granholm, E., Martone, M. (1986). An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. *Cortex*, *22*, 11-32. DOI: 10.1016/S0010-9452(86)80030-2

Butters, M.A., Glisky, E.L., & Schacter, D.L. (1993). Transfer of new learning in memory impaired patients. *Journal of Clinical and Experimental Neuropsychology, 15*, 219–230. DOI:10.1080/01688639308402559

Cadieux, N.L., Greve, K.W. (1997). Emotion processing in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *3*, 411-419.

Caldwell J.I. & Masson M.E. (2001). Conscious and unconscious influences of memory for object location. *Memory & Cognition, 29*, 285–295. DOI: 10.3758/BF03194922

Cermak, L., Butters, N., Goodglass, H. (1971). The extent of memory loss in Korsakoff patients. *Neuropsychologia*, *9*, 307-315.

Cermak, L.S., Lewis, R., Butters, N., Goodglass, H. (1973). Role of verbal mediation in performance of motor tasks by Korsakoff patients. *Perceptual and Motor Skills*, *37*, 259-262. DOI: 10.2466/pms.1973.37.1.259

Cermak L.S., Verfaellie M., Milberg W., Letourneau L., & Blackford S. (1991). A further analysis of perceptual identification priming in alcoholic Korsakoff patients. *Neuropsychologia*, *29*, 725-736. DOI:10.1016/0028-3932(91)90068-J

Chalfonte B.L., Verfaellie M., Johnson M.K., & Reiss L. (1996). Spatial location memory in amnesia: binding item and location information under incidental and intentional encoding conditions. *Memory, 4*, 591-614. DOI:10.1080/741940998

Charness, N., Milberg, W., Alexander, M.P. (1988). Teaching an amnesic a complex cognitive skill. *Brain and Cognition*, *8*, 253-272. DOI: 10.1016/0278-2626(88)90053-X

Christensen, H., Hazdi - Pavlovic, D., & Jacomb, P. (1991). The psychometric differentiation of dementia from normal aging: A meta-analysis. *Psychological Assessment*, *3*, 147–155. DOI: 10.1037/1040-3590.3.2.147

Chun, M.M. & Jiang, Y. (1998). Contextual cueing: Implicit learning and memory of visual context guides spatial attention. *Cognitive Psychology, 36*, 28–71. DOI: 10.1006/cogp.1998.0681

Chun, M.M. & Phelps, E.A. (1999). Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. *Nature Neuroscience, 2*, 844-847. DOI:10.1038/12222

Chun, M.M. (2000). Contextual cueing of visual attention. *Trends in Cognitive Sciences, 4*, 170-178. DOI: 10.1016/S1364-6613(00)01476-5

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., et al. (2011). Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Archives of Physical Medicine and Rehabilitation*, *92*, 519–530. DOI: 10.1016/j.apmr.2010.11.015

Clare L., & Jones R.S. (2008). Errorless learning in the rehabilitation of memory impairment: a critical review. *Neuropsychology Review*, *18*, 1-23. DOI:10.1007/s11065-008-9051-4a

17. DOI: 10.1007/s11065-008-9051-4

Cohen, N.J., Squire, L.R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, *210*, 207-210. DOI: 10.1126/science.7414331

Cohen, M., Ylvisaker, M., Hamilton, J., Kemp, L., & Claiman, B. (2010). Errorless learning of functional life skills in an individual with three aetiologies of severe memory and executive function impairment. *Neuropsychological Rehabilitation, 20*, 355–376. DOI:10.1080/09602010903309401

Cornell, E.H., Heth, C.D., & Alberts, D.M. (1994). Place recognition and way finding by children and adults. *Memory & Cognition, 22*, 633–643. DOI: 10.3758/BF03209249

Cullen, B., O'Neill, B., Evans, J.J., Coen, R.F., & Lawlor, B.A. (2007). A review of screening tests for cognitive impairment. *Journal of Neurology Neurosurgery and Psychiatry*, *78,* 790-799. DOI: 10.1136/jnnp.2006.095414

Day, E., Bentham, P., Callaghan, R., Kuruvilla, T., & George, S. (2004). Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse.

Cochrane database of systematic reviews (Online), *(1)*, CD004033

Davies, A.D.M., Binks, M.G. (1983). Supporting the residual memory of a Korsakoff patient. *Behavioural Psychotherapy*, *11*, 62-74.

Douglas, J.J., Wilkinson, D.A. (1993). Evidence of normal emotional responsiveness in alcoholic Korsakoff's syndrome in the presence of profound memory impairment. *Addiction*, *88*, 1637–1645. DOI: 10.1111/j.1360-0443.1993.tb02038.

de Fatima Alves Monteiro, M., Prado Bolognani, S.A., Strahler Rivero, T., Amodeo Bueno, O.F. (2011). Neuropsychological intervention in a case of Korsakoff's Amnesia. *Brain Impairment*, *12*, 231-238. DOI: 10.1375/brim.12.3.231

de Lange, L., Meertens, R., Smits, C. (2001). *Care Program Korsakoff's syndrome (in Dutch)*. Trimbos-instituut, Utrecht, The Netherlands

de Joode E.A., van Boxtel MP, Hartjes P, Verhey FR, van Heugten CM. (2013). Use of an electronic cognitive aid by a person with Korsakoff syndrome. *Scandinavian Journal of Occupational Therapy, 20*, 446-453. DOI: 10.3109/11038128.2013.821161.

De Wardener H.E., & Lennox B. (1947). Cerebral beriberi (Wernicke's Encephalopathy): review of 52 cases in a Singapore prisoner-of war hospital. *The Lancet, 1*,11-17. DOI: 10.1016/S0140-6736(47)91272-5

Dechamps, A., Fasotti, L., Jungheim, J., Leone, E., Dood, E., Allioux, A., Robert, P.H., Gervais, X., Maubourguet, N., Olde Rikkert, M.G., & Kessels, R.P.C. (2011). Effects of different learning methods for instrumental activities of daily living in patients with Alzheimer's dementia: a pilot study. *American Journal of Alzheimer's Disease and Other Dementias*, *26,* 273-281. DOI:10.1177/1533317511404394

Demirci, M., Grill, S., McShane, L., & Hallett, M. (1997). A mismatch between kinesthetic and visual perception in Parkinson's disease. *Annals of Neurology, 41*, 781-788. DOI: 10.1002/ana.410410614

d'Ydewalle, G., & Van Damme, I. (2007). Memory and the Korsakoff syndrome: not remembering what is remembered. *Neuropsychologia*, *45*, 905–920. DOI: 10.1016/j.neuropsychologia.2006.08.025

Egger, J.I.M., Wester, A.J., De Mey, H.R.A., Derksen, J.L. (2002). Korsakoff's syndrome on the MMPI-2. *Acta Neuropsychiatrica, 14*, 231-236. DOI: 10.1034/j.1601-5215.2002.140506.x

Ehlhardt, L.A., Sohlberg, M.M., Kennedy, M., Coehlo, C., Ylvisaker, M., Turkstra, L., & Yorkston, K. (2008). Evidence-based practice guidelines for instructing individuals with acquired memory impairments: what have we learned in the past 20 years? *Neuropsychological Rehabilitation*, *18*, 300–342. DOI: 10.1080/09602010701733190

Emery, C.F., Frid, D.J., Engebretson, T.O., Alonzo, A.A., Fish, A., Ferketich, A.K., Reynolds, Dujardin, J.P., Homan, J.E., Stern, S.L. (2004). Gender differences in quality of life among cardiac patients. *Psychosomatic Medicine*, *66*, 190-197. DOI: 10.1097/01.psy.0000116775.98593.f4

Eslinger, P.J., Damasio, A.R. (1986). Preserved motor learning in Alzheimer's disease: implications for anatomy and behavior. *Journal of Neuroscience, 6*, 3006-3009.

Ettema T.P., Dröes, R.M., de Lange, J., Mellenbergh, G.J., Ribbe, M.W. (2005a). A review of quality of life instruments used in dementia. *Quality of Life Research*, *14*, 675-686. DOI: 10.1007/s11136-004-1258-0

Ettema, T.P., de Lange, J., Droës, R.M., Mellenbergh, G.J., Ribbe, M.W. (2005b). *Qualidem Manual (in Dutch)*. Trimbos Institute, Amsterdam, The Netherlands.

Ettema, T.P., Dröes, R.M., de Lange, J., Mellenbergh, G.J., Ribbe, M.W. (2007a). QUALIDEM: development and evaluation of a dementia specific quality of life instrument. Scalability, reliability and internal structure. *International Journal of Geriatric Psychiatry*, *22*, 549-556. DOI: 10.1002/gps.1713

Ettema, T.P., Dröes, R.M., de Lange, J., Mellenbergh, G.J., Ribbe, M.W. (2007b). QUALIDEM: development and evaluation of a dementia specific quality of life instrument - validation. *International Journal of Geriatric Psychiatry*, *22*, 424-430. DOI: 10.1002/gps.1692

Evans, J.J., Wilson, B.A., Schuri, U., Andrade, J., Baddeley, A., Bruna, O., Canavan, T., Del Sala, S., Green, R., Laaksonen, R., Lorenzi, L., & Taussik, I. (2000). A comparison of "errorless" and "trial-and-error" learning methods for teaching individuals with acquired memory deficits. *Neuropsychological Rehabilitation*, *10*, 67-101. DOI: 10.1080/096020100389309

Fama R., Pfefferbaum A., & Sullivan E.V. (2006). Visuoperceptual learning in alcoholic Korsakoff syndrome. *Alcoholism: Clinical & Experimental Research*, *30*, 680-687. DOI:10.1111/j.1530-0277.2006.00085.x

Ferran, J., Wilson, K., Doran, M., Ghadiali, E., Johnson, F., Cooper, P. McCrackens, C. (1996). The early onset dementias: A study of clinical and service need. *International Journal of Geriatric Psychiatry*, *11*, 863–869. DOI: 10.1002/(SICI)1099-1166(199610)11:10<863::AID-GPS394>3.0.CO;2-7

Fillingham J.K., Sage K., & Ralph M.A. (2005). Treatment of anomia using errorless versus errorful learning: are frontal executive skills and feedback important? *International Journal of Language and Communication Disorders*, *40*, 505-523. DOI: 10.1080/13682820500138572

Feigenbaum, J.D., Polkey, C.E., & Morris, R.G. (1996). Deficits in spatial working memory after unilateral temporal lobectomy in man. *Neuropsychologia, 34*, 163–176. DOI: 10.1016/0028-3932(95)00107-7

Folstein M.F., Folstein S.E., & McHugh P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, *12*, 189–198. DOI:10.1016/0022-3956(75)90026-6.

Fujiwara, E., Brand, M., Borsutzky, S., Steingass, H.-P. & Markowitsch, H.J. (2008). Cognitive performance of detoxified alcoholic Korsakoff syndrome patients remains stable over two years. *Journal of Clinical and Experimental Neuropsychology, 30,* 576-587. DOI: 10.1080/13803390701557271

Ganzevles, P.G.J., De Geus, B.W.J. & Wester, A.J. (1994). Cognitive and behavioral aspects of Korsakoff's syndrome: The effect of special Korsakoff's wards in general psychiatric hospital. (in Dutch). *Tijdschrift voor Alcohol, Drugs en Andere Psychotrope Stoffen, 20*, 20-31.

Gerridzen, I.J., Goossensen, M.A. (2014). Patients with Korsakoff syndrome in nursing homes: characteristics, comorbidity, and use of psychotropic drugs. *International Psychogeriatrics, 26*, 115-121.

Gluhm, S., Goldstein, J., Brown, D., Van Liew, C., Gilbert, P. E., & Corey-Bloom, J. (2013). Usefulness of the Montreal Cognitive Assessment (MoCA) in Huntington's disease. *Movement Disorders*, *28*, 1744-1747. DOI: 10.1002/mds.25578

Goldstein S., & Naglieri J. A. (2014). *Handbook of Executive Functioning*. Dordrecht: Springer

Goossensen, A., Arts, K., Beltman, M. (2007). *Care Program Korsakoff's syndrome in nursing homes "Nothing Wrong With Me"* (in Dutch). Korsakoff Knowledge Center, Utrecht, The Netherlands.

Graaf, de, A., & Deelman, B.G. (1991). *Cognitive Screening Test Manual (in Dutch).* Lisse: Swets & Zeitlinger.

Graf, P., Shimamura, A.P., & Squire, L.R. (1985). Priming across modalities and priming across category levels: Extending the domain of preserved function in amnesia. *Journal of Experimental Psychology, Learning, Memory, and Cognition*, *11*, 386–396. DOI: 10.1037/0278-7393.11.2.386

Greenaway, M.C., Duncan, N.L., Smith, G.E. (2013). The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. *International Journal of Psychiatry*, *28*, 402-409. DOI : 10.1002/gps.3838

Hammes, J.G.W. (1971). *De Stroop Color WordTest Manual (in Dutch).* Lisse: Swets en Zeitlinger.

Harper, C.G., Giles, M., & Finlay-Jones, R. (1986). Clinical signs in the Wernicke-Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. Journal of Neurology Neurosurgery and Psychiatry, 49, 341-345. DOI: 10.1136/jnnp.49.4.341

Harper, C., Gold, J., Rodriguez, M., Perdices, M. (1989). The prevalence of the Wernicke-Korsakoff syndrome in Sydney, Australia: A prospective necropsy study. *Journal of Neurology Neurosurgery and Psychiatry*, *52*, 282-285. DOI: 10.1136/jnnp.52.2.282

Harper, C.G., Sheedy, D.L., Lara, A.I., Garrick, T.M., Hilton, J.M., Raisanen, J. (1998). Prevalence of Wernicke-Korsakoff syndrome in Australia: has thiamine fortification made a difference? *Medical Journal of Australia*, *168*, 542-545.

Hasher, L., & Zacks, R.T. (1979). Automatic and effortful processes in memory. *Journal of Experimental Psychology: General, 108*, 356–388. DOI: 10.1037//0096-3445.108.3.356

Hassin, R.R., Bargh, J.A., Engell, A.D. & McCulloch, K.C. (2009). Implicit working memory. *Consciousness and Cognition, 18*, 665-678. DOI: 10.1016/j.concog.2009.04.003

Haxby, J.V., Ludgren, S.L. & Morley, G.K. (1983). Short-term retention of verbal, visual shape, and visuospatial location information in normal and amnesic subjects. *Neuropsychologia, 21*, 25-33. DOI: 10.1016/0028-3932(83)90097-0

Hayes, S.M., Fortier, C.B., Levine, A., Milberg, W.P., & McGlinchey, R. (2012). Implicit memory in Korsakoff's syndrome: A review of procedural learning and priming studies. *Neuropsychology Review*, *22*, 132-153. DOI: 10.1007/s11065-012-9204-3

Heindel, W.C., Butters, N., Salmon, D.P. (1988). Impaired Learning of a Motor Skill in Patients With Huntington's Disease. *Behavioral Neuroscience, 102* , 141-147. DOI: 10.1037/0735-7044.102.1.141

Hochstenbach, J., Mulder, T., Van Limbeck, J., Donders, R., & Schoonderwaldt, H. (1998). Cognitive decline following stroke: A comprehensive study of cognitive decline following stroke. *Journal of Clinical and Experimental Neuropsychology*, *20*, 503-517. DOI: 10.1076/jcen.20.4.503.1471

Holdstock, J.S., Mayes, A.R., Cezayirli, E., Aggleton, J.P. & Robberts, N. (1999). A comparison of egocentric and allocentric spatial memory in medial temporal lobe and Korsakoff amnesics. *Cortex, 35*, 479-501. DOI: 10.1101/lm.122206

Hoops, S., Nazem, S., Siderowf, A. D.,, Duda, J. E., Xie, S. X., Stem, M.B., Weintraub, D. (2009). Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology, 73*, 1738–1745. DOI:10.1212/WNL.0b013e3181c34b47

Horton, L., Duffy, T., Martin, C. (2014). Interventions for alcohol-related brain damage (ARBD): Do specific approaches restrict the evolution of comprehensive patient care? *Drugs: Education, Prevention, and Policy*, *21*, 408-419. DOI: 10.3109/09687637.2014.924481

Ioannidis, J. P. A. (2005). Why most published research findings are false. PLoS Medicine, 2, 696–701. DOI:10.1371/journal.pmed.0020124

Isenberg-Grzeda, E., Kutner, H. E., & Nicolson S. E. (2012). Wernicke-Korsakoff-syndrome: under-recognized and under-treated. *Psychosomatics, 53,* 507-516. DOI: 10.1016/j.psym.2012.04.008

Isenberg-Grzeda E., Chabon B., & Nicolson S.E. (2014). Prescribing Thiamine to Inpatients, With Alcohol Use Disorders: How Well Are We Doing? *Journal of Addiction Medicine*, *8*, 1-5. DOI: 10.1097/01.ADM.0000435320.72857.c8

Jacobson, R.R., & Lishman, W.A. (1987). Selective memory loss and global intellectual deficits in alcoholic Korsakoff's syndrome. *Psychological Medicine*, *17*, 649-655. DOI: 10.1017/S0033291700025885

Jacobsen, R.R., Acker, C.F., & Lishman, W. (1990). Patterns of neuropsychological deficits in alcoholic Korsakoff's syndrome. *Psychological Medicine*, *20*, 321–334. DOI: 10.1017/S0033291700017633

Jiang, Y., Song, J.H., & Rigas A. (2005) High-capacity spatial contextual memory. *Psychonomic Bulletin and Review, 12*, 524-529. DOI: 10.3758/BF03193799

Joyce, E.M., Robbins, T.W. (1991). Frontal lobe function in Korsakoff and non-Korsakoff alcoholics: Planning and spatial working memory. *Neuropsychologia*, *29*, 709-723. DOI: 10.1016/0028-3932(91)90067-I

Jung, Y.-C., Chanraud, S., & Sullivan, E.V. (2012). Neuroimaging of Wernicke's Encephalopathy and Korsakoff's Syndrome. *Neuropsychology Review, 22*, 170-180. DOI: 10.1007/s11065-012-9203-4

Kafer, K.L & Hunter, M. (1997). On testing the face validity of planning/problem-solving tasks in a normal population. *Journal of the International Neuropsychological Society, 3*, 108-119.

Kaya, Y., Aki, O.E., Can, U.A., Derle, E., Kibaro, S., & Barak, A. (2014). Validation of Montreal Cognitive Assessment and Discriminant Power of Montreal Cognitive Assessment Subtests in Patients With Mild Cognitive Impairment and Alzheimer Dementia in Turkish Population. *Journal of Geriatric Psychiatry and Neurology, 27,* 103-107. DOI: 10.1177/0891988714522701

Kemp, B., Ettelson, D. (2001). Quality of life while living and aging with a spinal cord injury and other impairments. *Topics in Spinal Cord Injury Rehabilitation*, *6*, 116–127. DOI: 10.1310/L8TF-65XD-8K1U-UE3M

Kessels, R.P.C., Postma, A., de Haan, E.H. (1999). Object Relocation: a program for setting up, running, and analyzing experiments on memory for object locations. *Behavior research methods, instruments, & computers: a journal of the Psychonomic society*, *31*, 423-428. DOI: 10.3758/BF03200721

Kessels, R.P.C., van Zandvoort, M.J.E., Postma, A., Kappelle, L.J. & De Haan, E.H.F. (2000). The Corsi Block-Tapping Task: Standardization and normative data. *Applied Neuropsychology*, *7*, 252-258. DOI:10.1207/S15324826AN0704_8

Kessels R.P.C., Postma A., Wester A.J., & de Haan, E.H.F. (2000). Memory for object locations in Korsakoff's amnesia. *Cortex*, *36*, 47-57. DOI:10.1016/S0010-9452(08)70835-9

Kessels R.P.C., & de Haan, E.H.F. (2000). Implicit learning in memory rehabilitation: a meta-analysis on errorless learning and vanishing cues methods. *Journal of Clinical and Experimental Neuropsychology*, *25,* 805-814. DOI:10.1076/jcen.25.6.805.16474

Kessels, R.P.C., de Haan, E.H.F., Kappelle, L.J., & Postma, A. (2002). Selective impairments in spatial memory after ischaemic stroke. *Journal of Clinical and Experimental Neuropsychology, 24*, 115-129. DOI: 10.1076/jcen.24.1.115.967

Kessels R.P.C, Boekhorst S.T., & Postma, A. (2005). The contribution of implicit and explicit memory to the effects of errorless learning: a comparison between young and older adults. *Journal of the International Neuropsychological Society*, *11*, 144-151. DOI:10.1017/S1355617705050174

Kessels, R.P.C., Nys, G.M.S., Brands, A.M.A., van den Berg, E., & Van Zandvoort, M.J.E. (2006). The modified Location Learning Test: Norms for the assessment of spatial memory function in neuropsychological patients. *Archives of Clinical Neuropsychology, 21*, 841-846. DOI: 10.1016/j.acn.2006.06.015

Kessels R.P.C., van Loon E., & Wester A.J. (2007). Route learning in amnesia: a comparison of trial-and-error and errorless learning in patients with the Korsakoff syndrome. *Clinical Rehabilitation*, *21*, 905-911. DOI:10.1177/0269215507077309

Kessels, R.P.C., Van Den Berg, E., Ruis, C., & Brands, A.M. (2008). The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment*, *15*, 426-434. DOI:10.1177/1073191108315611

Kessels, R.P.C., Kortrijk, H.E., Wester, A.J., & Nys, G.S. (2008). Confabulation behavior and false memories in Korsakoff's syndrome: Role of source memory and executive functioning. *Psychiatry and Clinical Neurosciences, 62*, 220-225. DOI: 10.1111/j.1440-1819.2008.01758.x

Kessels, R.P.C., Meulenbroek, O., Fernandez, G., & Olde Rikkert, M.G.M. (2010). Spatial working memory in aging and mild cognitive impairment: Effects of task load and contextual cueing. *Aging, Neuropsychology, and Cognition, 17*, 556-574. DOI: 10.1080/13825585.2010.481354

Kessels, R.P.C., van Doormaal, A., & Janzen, G. (2011). Landmark recognition in Alzheimer's dementia: Spared implicit memory for objects relevant for navigation. *Plos ONE, 6, e18611*. DOI:10.1371/journal.pone.0018611

Kessels, R.P.C., Bucks, R.S. , Willison, J.R. , & Byrne, L.M.T . (2012). *Location learning test: Manual* . Bury St. Edmunds, UK : Thames Valley Test Company.

Kessels, R.P.C., & Kopelman, M.D. (2012). Context memory in Korsakoff's syndrome. *Neuropsychology Review, 22*, 117-131. DOI: 10.1007/s11065-012-9202-5

Klimkowicz-Mrowiec, A., Slowik, A., Krzywoszanski, L., Herzog-Krzywoszanska, R., & Szczudlik, A. (2008). Severity of explicit memory impairment due to Alzheimer's disease improves effectiveness of implicit learning. *Journal of Neurology, 255*, 502–509. DOI:10.1007/s00415-008-0717-x

Kok A.F. (1991). Developments in the care of Korsakoff patients (in Dutch). *Tijdschrift voor Alcohol, Drugs en Andere Psychotrope Stoffen*, *17*, 3–9.

Kok, R.M., Verhey, F.R.J., & Schmand, B (2004). Measurements for cognitive disorders (in Dutch) *Tijdschrift voor Psychiatrie*, *46*, 665-669.

Komatsu, S.-I., Mimura, M., Kato, M., Wakamatsu, N., & Kashima, H. (2000). Errorless and effortful processes involved in the learning of face–name associations by patients with alcoholic Korsakoff's syndrome. *Neuropsychological Rehabilitation, 10*, 113–132. doi:10.1080/096020100389200

Kopelman, M.D. (1991). Non-verbal, short-term forgetting in the alcoholic Korsakoff syndrome and Alzheimer-type dementia. *Neuropsychologia*, *29*, 737-747. DOI:10.1016/0028-3932(91)90069-K

Kopelman, M.D. (1995). The Korsakoff syndrome. *British Journal of Psychiatry*, *166*, 154-173. DOI:10.1192/bjp.166.2.154

Kopelman, M. D., Stanhope, N., & Kingsley, D. (1999). Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions. *Neuropsychologia, 37*, 939–958. DOI: 10.1016/S0028-3932(98)00143-2

Kopelman, M.D. (2002). Disorders of memory. *Brain*, *125*, 2152-2190. DOI: 10.1093/brain/awf229

Kopelman, M.D., Thomson, A.D., Guerrini, I., & Marshall, E.J. (2009). The Korsakoff Syndrome: Clinical Aspects, Psychology and Treatment. *Alcohol & Alcoholism, 44*, 148-154. DOI: 10.1093/alcalc/agn118

Korsakoff, S.S. (1887). Disturbance of psychic function in alcoholic paralysis and its relation to the disturbance of the psychic sphere in multiple neuritis of non-alcoholic origin. Quoted by Victor, M., Adams, R.D., Collins, G.H. (1971). The Wernicke–Korsakoff Syndrome. Philadelphia, F.A. Davis.

Korsakoff, S.S. (1889). Psychic disorder in conjunction with peripheral neuritis. Translated by Victor, M., Yakovlev, P.I. (1955). *Neurology*, 5, 394–406. DOI: 10.1212/WNL.5.6.394

Komatsu, S.-I., Mimura, M., Kato, M., Wakamatsu, N., & Kashima, H. (2000). Errorless and effortful processes involved in the learning of face–name associations by patients with alcoholic Korsakoff's syndrome. *Neuropsychological Rehabilitation*, *10*, 113-132. DOI:10.1080/096020100389200

Kril, J.J., Harper, C.G. (2012). Neuroanatomy and neuropathology associated with Korsakoff's syndrome. *Neuropsychology Review, 22*, 72-80. DOI: 10.1007/s11065-012-9195-0

Lee, J.Y., Lee, D.W., Cho, S.J., Na, D.L., Jeon, H.J., Kim, S.K, Lee, Y.R., Kwon, M., Lee, J.-H., & Cho, M.J. (2008). Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal cognitive assessment. *Journal of Geriatric Psychiatry and Neurology, 21,* 104-110. DOI: 10.1177/0891988708316855

Lekeu, F., Wojtasik, V., Van der Linden, M., & Salmon, E. (2002). Training early Alzheimer patients to use a mobile phone. *Acta Neurologica Belgica, 102*, 114–121.

Lezak, M.D. (1995). *Neuropsychological Assessment (3rd ed.).* New York: Oxford University Press.

Li, R., & Liu, K.P. (2012). The use of errorless learning strategies for patients with Alzheimer's disease: a literature review. *International Journal of Rehabilitation Research*, *35*, 292-298. DOI: 10.1097/MRR.0b013e32835a2435

Light, L.L., & Zelinski, E.M. (1983). Memory for spatial information in young and old adults. *Developmental Psychology, 19*, 901–906. DOI: 10.1037//0012-1649.19.6.901

Lindeboom, J., Schmand, B, Tulner, L., Walstra, G., & Jonker, C. (2002). Visual association test to detect early dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery and Psychiatry, 73*, 126-133. DOI: 10.1136/jnnp.73.2.126

Lough, M.E. (2012). Wernicke's Encephalopathy: Expanding the Diagnostic Toolbox. *Neuropsychology Review, 22,* 181-194. DOI: 10.1007/s11065-012-9200-7

Maharasingam, M., Macniven, J.A., & Mason, O.J. (2013). Executive functioning in chronic alcoholism and Korsakoff syndrome. *Journal of Clinical and Experimental Neuropsychology*, *35,* 501-508. DOI: 10.1080/13803395.2013.795527

Manns, J.R. & Squire, L.R. (2001). Perceptual learning, awareness, and the hippocampus. *Hippocampus 11*, 776-782. DOI: 10.1002/hipo.1093

Manzo, L., Locatelli, C., Candura, S.M., & Costa, LG. (1994). Nutrition and alcohol neurotoxicity. *Neurotoxicology,* 15, 555–565.

Martone, M., Butters, N., Payne, M., Becker, J.T., Sax, D.S. (1984). Dissociation between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology, 41*, 965-970. DOI:10.1001/archneur.1984.04050200071020.

Mayes, A.R., Meudell, P.R. & MacDonald, C. (1991). Disproportionate intentional spatial-memory impairments in amnesia. *Neuropsychologia, 29*, 771-784. DOI: 10.1016/0028-3932(91)90071-F

Mayes, A.R., Daum, I., Markowisch, H.J., Sauter, B. (1997). The Relationship between Retrograde and Anterograde Amnesia in Patients with Typical Global Amnesia. *Cortex*, *33*, 197-217. DOI: 10.1016/S0010-9452(08)70001-7

McEntee, W.J., Mair, R.G., Langlais, P.J. (1987). Neurochemical specificity of learning: Dopamine and motor learning. *Yale Journal of Biology and Medicine, 60*, 187-193.

McGurn, B., Starr, J.M., Topfer, J.A., Pattie, A., Whiteman, M.C., Lemmon, H.A., Whalley, L.J., & Deary, I.J. (2004). Pronunciation of irregular words is preserved in dementia, validating premorbid IQ estimation. *Neurology*, *62*, 1184–1186. DOI: 10.1212/01.WNL.0000103169.80910.8B

Meulenbroek, O., Vernooij-Dassen, M., Kessels, R.P.C., Graff, M.J.L, Sjögren, M.J.C., Schalk, B.W.M., Hoogsteen-Ossewaarde, M.E., Claassen, J.A.H.R., Melis, R.J.F., & Olde Rikkert, M.G.M. (2010). Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent. *European Geriatric Medicine, 1*, 58-63. DOI: 10.1016/j.eurger.2010.01.009

Meyers, J.E., & Meyers, K.R. (1995). *Rey Complex Figure Test and Recognition Trial (RCFT). Professional Manual*. Lutz: Psychological Assessment Resources, Inc.

Mickes, L., Jacobson, M., Peavy, G., Wixted, J.T., Lessig, S., Goldstein, J.L., & Corey-Bloom, J. (2009). A comparison of two brief screening measures of cognitive impairment in Huntington's disease. *Movement Disorders*, *25*,2229-2233. DOI: 10.1002/mds.23181

Mimura, M., Kinsbourne, M., & O'Connor, M. (2000). Time estimation by patients with frontal lesions and by Korsakoff amnesics. *Journal of the International Neuropsychological Society, 6*, 517-528. DOI: 10.1017/S1355617700655017

Mioshi, E., Hsieh, S., Savage, S., Hornberger, M., & Hodges, J.R. (2010). Clinical staging and disease progression in frontotemporal dementia. *Neurology, 74*, 1591-1597. DOI: 10.1212/WNL.0b013e3181e04070.

Mitchell, A. J. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of Psychiatric Research*, *43,* 411-431. DOI: 10.1016/j.jpsychires.2008.04.014

Morgan J, McSharry K, Sireling L. (1990). Comparison of a system of staff prompting with a programmable electronic diary in a patient with Korsakoff's syndrome. *International Journal of Social Psychiatry, 36*, 225-229. DOI: 10.1177/002076409003600308

Morris, R., Evenden, J., Sahakian, B., & Robbins, T. (1987). Computer-aided assessment of dementia: Comparative studies of neuropsychological deficits in Alzheimer-type dementia and Parkinson's disease. In Stahl, S., Iversen, S., & Goodman, E. (Eds.), *Cognitive neurochemistry* 21–36. Oxoford, UK: Oxford University Press.

Mulder, J.L., Dekker, R., & Dekker, P.H. (1996). *Verbale Leer en Geheugen Test: Handleiding*. Lisse: Swets & Zeitlinger.

Mulder, J.L, Dekker, P.H., & Dekker, R. (2006). *Word-Fluency Test (in Dutch)*. PITS uitgeverij BV, Leiden.

Nagel., B.J., Ohanessian, A., Cummins, K. (2007). Performance dissociation during verbal and spatial working memory tasks. *Perceptual and Motor Skills*, *105*, 243-250. DOI: 10.2466/PMS.105.1.243-250.

Nasreddine, Z.S., Phillips, N.A., Be´dirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L, & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatric Society*, *52*, 695–699. DOI: 10.1111/j.1532-5415.2005.53221.x

Netuveli, G., Wiggins, R.D., Hildon, Z., Montgomery, S.M., Blane, D. (2006). Quality of life at older ages: Evidence from the English longitudinal study of aging (wave 1). *Journal of Epidemiology and Community Health*, *60*, 357–363. DOI: 10.1136/jech.2005.040071

Nissen, M.J., Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology, 19*, 1-32. DOI: 10.1016/0010-0285(87)90002-8

Nissen, M.J., Willingham, D., & Hartman, M. (1989). Explicit and implicit remembering: When is learning preserved in amnesia? *Neuropsychologia*, *27*, 341-352. DOI: 10.1016/0028-3932(89)90023-7

Norris, G., & Tate, R.L. (2000). The Behavioural Assessment of the Dysexecutive Syndrome (BADS): ecological, concurrent and construct validity. *Neuropsychological Rehabilitation, 10*, 33-45. doi : 10.1080/096020100389282

Nys, G.M.S., van Zandvoort, M.J.E., de Kort, P.L.M., Jansen, B.P.W., Kappelle, L.J., & de Haan, E.H. F. (2005). Restrictions of the Mini-Mental State Examination in acute stroke. *Archives of Clinical Neuropsychology, 20,* 623-629. DOI: 10.1016/j.acn.2005.04.001

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*, 97-113. DOI: 10.1016/0028-3932(71)90067-4

Oscar-Berman, M., Zola-Morgan, S.M., Oberg, R.G., Bonner, R.T. (1982). Comparative neuropsychology and Korsakoff's syndrome. III--Delayed response, delayed alternation and DRL performance. *Neuropsychologia, 20*, 187-202. DOI: 10.1016/0028-3932(82)90009-4

Oscar-Berman, M., Hutner, N., & Bonner, R. T. (1992). Visual and auditory spatial and nonspatial delayed-response performance by Korsakoff and non-Korsakoff alcoholic and aging individuals. *Behavioral Neuroscience*, *106*, 613–622. DOI: 10.1037/0735-7044.106.4.613

Oscar-Berman, M. (2012). Function and dysfunction of prefrontal brain circuitry in alcoholic Korsakoff's syndrome. *Neuropsychology Review, 22*, 154–169. DOI: 10.1007/s11065-012-9198-x

Oslin, D., Atkinson, R.M., Smith, D.M., & Hendrie, H. (1998). Alcohol related dementia: Proposed clinical criteria. *International Journal of Geriatric Psychiatry*, *13*, 203-212. DOI: 10.1097/00019442-200307000-00007

Ostergaard A.L. (1999). Priming deficits in amnesia: now you see them, now you don't. *Journal of International Neuropsychological Society 5*, 175–190. DOI: 10.1017/S1355617799533018

Oudman, E., Van der Stigchel S., Wester A.J., Kessels R.P.C., & Postma A. (2011). Intact memory for implicit contextual information in Korsakoff's amnesia. *Neuropsychologia*, *49*, 2848-2855. DOI:10.1016/j.neuropsychologia.2011.06.010

Oudman, E., & Zwart, E. (2012). Quality of life of patients with Korsakoff's syndrome and patients with dementia: a cross-sectional study. *Journal of the American Medical Directors Association*, *13*, 778-781. DOI: 10.1016/j.jamda.2012.08.003

Oudman E., Nijboer T.C.W., Postma A., Wijnia J.W., Kerklaan S., Lindsen K., & Van der Stigchel S. (2013). Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: A comparison of trial and error and errorless learning. *Neuropsychological Rehabilitation, 23,* 888-913. DOI: 10.1080/09602011.2013.835738

Oudman, E., & Wijnia, J.W. (2014). BNF Recommendations for the Treatment of Wernicke's Encephalopathy: Lost in Translation? *Alcohol and Alcoholism*, *49,* 118. DOI: 10.1093/alcalc/agt179

Oudman, E., Van der Stigchel, S., Postma, A., Wijnia, J.W., Nijboer, T.C.W. (2014). A Case of Chronic Wernicke's Encephalopathy: A Neuropsychological Study. *Frontiers in Psychiatry, 5*, 59. DOI: 10.3389/fpsyt.2014.00059

Paller, K.A., Acharya, A., Richardson, B.C., Plaisant, O., Shimamura, A.P., Reed, B.R. & Jagust, W.J. (1997). Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. *Journal of Cognitive Neuroscience, 9*, 277-293. DOI: 10.1162/jocn.1997.9.2.277

Page, M., Wilson, B. A., Shiel, A., Carter, G., & Norris, D. (2006). What is the locus of the errorless-learning advantage? *Neuropsychologia, 44*, 90–100. DOI:10.1016/j.neuropsychologia.2005.04.004

Passot, J.B., Sheynikhovich, D., Duvelle, E., Arleo, A. (2012). Contribution of cerebellar sensorimotor adaptation to hippocampal spatial memory. *PloS one, 7*, e32560. DOI: 10.1371/journal.pone.0032560

Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., de la Sayette, V., Viader, F., Desgranges, B. & Eustache, F. (2008). Episodic and working memory deficits in alcoholic Korsakoff patients: the continuity theory revisited. *Alcoholism: Clinical and Experimental Research, 32,* 1229-1241.

Pitel, A.L., Chételat, G., Le Berre, A.P., Desgranges, B., Eustache, F., & Beaunieux, H. (2012). Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated alcoholism. *Neurology*, *78*, 1330-1333. DOI: 10.1212/WNL.0b013e318251834e

Popoola, A., Keating, A., & Cassidy, E. (2008). Alcohol, cognitive impairment and the hard to discharge acute hospital inpatients. *Irish Journal of Medical Science, 117,* 141-145. DOI: 10.1007/s11845-008-0135-1

Postma A., Van Asselen M., Keuper O., Wester A.J., & Kessels R.P.C. (2006). Spatial and temporal order memory in Korsakoff patients. *Journal of the International Neuropsychological Society*, *12*, 327-336. DOI:10.1017/S1355617706060449

Postma, A., Kessels, R.P.C., van Asselen, M. (2008). How the brain remembers and forgets where things are: The neurocognition of object-location memory. *Neuroscience and Biobehavioral Reviews*, *32*, 1339-1345. DOI: 10.1016/j.neubiorev.2008.05.001

Postma A., Antonides R., Wester A.J., & Kessels R.P.C. (2008). Spared unconscious influences of spatial memory in diencephalic amnesia. *Experimental Brain Research*, *190*, 125-133. DOI:10.1007/s00221-008-1456-z

Postma, A., van Oers, M., Back, F., & Plukaard, S. (2012). Losing Your Car in the parking lot: Spatial Memory in the Real World. *Applied Cognitive Psychology, 26*, 680-686. DOI: 10.1002/acp.2844

Provencer V., Bier N., & Audet T. (2008). Errorless-based techniques can improve route finding in early Alzheimer's disease: a case study. *American Journal of Alzheimer's Disease and Other Dementias*, *23*, 47-56. DOI:10.1177/1533317507307228

Ptak R, Van der Linden MV, & Schnider A. (2010). Cognitive rehabilitation of episodic memory disorders: from theory to practice. *Frontiers in Human Neuroscience*, *14*, 57. DOI: 10.3389/fnhum.2010.00057

Quick, H.E., Moen, P. (1998). Gender, employment, and retirement quality: A life course approach to the differential experiences of men and women. *Journal of Occupational Health Psychology*, *3*, 44-64. DOI: 10.1037/1076-8998.3.1.44

Ramayya, A., Jauhar, P. (1997). Increasing incidence of Korsakoff's psychosis in the east end of Glasgow. *Alcohol and Alcoholism*, *32*, 281-285. DOI: 10.1093/alcalc/33.5.550

Raven, J., Raven, J.C., & Court, J.H. (1995) *General overview*. Oxford, Oxford University press LTD.

Rees, L., Marshall, S., Hartridge, C., Mackie, D., and Weiser, M. (2007). Cognitive interventions fpost acquired brain injury. *Brain Injury*, *21*, 161–200. DOI: 10.1080/02699050701201813

Reisberg, B., Ferris, S.H., de Leon, M.J., Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry*, *139*, 1136-1139. DOI: 10.1176/ajp.139.9.1136

Rey, A. (1958). *L'examin clinique en psychologie.* Paris, France: Presses Universitaires de France

Riemersma - van der Lek, R.F., Swaab, D.F., Twisk, J., Hol, E.M., Hoogendijk, W.J., Van Someren, E.J. (2008). Effect of bright light and melatonin on cognitive and non-cognitive function in elderly residents of group care facilities: A randomized controlled trial. *JAMA*, *299*, 2642-2655. DOI: 10.1001/jama.299.22.2642.

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., & Rabbitt, P. (1994). Cambridge neuropsychological test automated battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. *Dementia, 5*, 266–281. DOI: 10.1159/000106735

Rodriguez - Fornells, A., Kofidis, C., & Munte, T.F. (2004). An electrophysiological study of errorless learning. *Cognitive Brain Research*, *19*, 160-173. DOI: 10.1016/j.cogbrainres.2003.11.009

Sacks, O.W. (1985). *The man who mistook his wife for a hat, and other clinical tales.* London: Duckworth.

Salamé, P., Danion, J.M., Peretti, S., & Cuervo, C. (1998). The state of functioning of working-memory in schizophrenia. *Schizophrenia Research*, *30*, 11-29. DOI: 10.1016/S0920-9964(97)00107-2

Schmand, B., Lindeboom, J., & van Harskamp, F. (1992). *Manual for the Dutch reading test for adults. Lisse, The Netherlands*: Swets & Zeitlinger.

Schmand, B., Houx, P., de Koning, I. (2012). Norms for Word Fluency, Stroop Color Word test, Trail Making Test, Verbal Learning Test, and Story Recall of Rivermead Behavioural Memory Test. Dutch Norms. Section Neuropsychology Dutch Institute of Psychologists, Amsterdam

Schmidt, I.W., Berg, I.J., & Deelman, B.G. (2001). Prospective memory training in older adults. *Educational Gerontology*, *27*, 455-471. DOI: 10.1080/036012701316894162

Schouten H.J., Knol W., Egberts T.C., Schobben A.F., Jansen P.A., van Marum R.J. (2012). Quality of life of elderly patients with antipsychotic-induced parkinsonism: A cross-sectional study. *Journal of the American Medical Directors Association*, *13*, 82.e1–82.e5. DOI: 10.1016/j.jamda.2012.08.003

Schölzel-Dorenbos, C.J., Ettema, T.P., Bos, J., Boelens-van der Knoop, E., Gerritsen, D.L., Hoogeveen, F., de Lange, J., Meihuizen, L., Dröes, R.M. (2007). Evaluating the outcome of interventions on quality of life in dementia: Selection of the appropriate scale. *International Journal of Geriatric Psychiatry*, *22*, 511-519. DOI: 10.1002/gps.1719

Scoville, W.B., Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 20*, 11-21. DOI:10.1136/jnnp.20.1.11

Sechi, G.P., & Serra A. (2007). Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurology*, *6*, 442-455. DOI:10.1016/S1474-4422(07)70104-7

Seger, C. A. (1994). Implicit learning. *Psychological Bulletin*, *115*, 163-196. DOI: 10.1037/0033-2909.115.2.163

Smith, I., & Hilman, A. (1999). Management of Alcohol Korsakoff Syndrome. *Advances in Psychiatry Treatment, 5*, 271-278. DOI:10.1192/apt.5.4.271

Spiers, H.J., Burgess, N., Maguire, E.A., Baxendale, S.A., Hartley, T., Thompson, P.J., & O'Keefe, J. (2001). Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. *Brain, 124*, 2476-2489. DOI: 10.1093/brain/124.12.2476

Spreij, L.A., Visser-Meily, J.M., van Heugten, C.M., Nijboer, T.C.W. (2014). Novel insights into the rehabilitation of memory post acquired brain injury: a systematic review. *Frontiers of Human Neuroscience*, *16*, 993. DOI: 10.3389/fnhum.2014.00993.

Squire, L.R. (1982). Comparisons between forms of amnesia: Some deficits are unique to Korsakoff's syndrome. *Journal of Experimental Psychology: Learning, Memory and Cognition, 8*, 560-571. DOI: 10.1037/0278-7393.8.6.560

Squire, L.R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory, 82*, 171-177. DOI: 10.1016/j.nlm.2004.06.005

Squire, L.R. (2009). Memory and Brain Systems: 1969-2009. *Journal of Neuroscience*, *29*, 12711–12716. DOI: 10.1523/JNEUROSCI.3575-09.2009

Stip, E. Rialle, V. (2005). Environmental cognitive remediation in schizophrenia: Ethical implications of "smart home" technology. *Canadian Journal of Psychiatry*, *50*, 281-291.

Sullivan, E.V. & Pfefferbaum, A. (2009). Neuroimaging of the Wernicke-Korsakoff syndrome. *Alcohol and Alcoholism, 44,* 155-165. DOI: 10.1093/alcalc/agn103

Svanberg, J., Evans, J.J. (2013). Neuropsychological rehabilitation in alcohol-related brain damage: a systematic review. *Alcohol and Alcoholism, 48*, 704-711. DOI: 10.1093/alcalc/agt131

Svanberg, J., Evans, J.J. (2014). Impact of SenseCam on memory, identity and mood in Korsakoff's syndrome: a single case experimental design study. *Neuropsychological Rehabilitation*, *24*, 400-418. DOI:10.1080/09602011.2013.814573

Swinnen, S.P., Puttemans, V., & Lamote, S. (2005). Procedural memory in Korsakoff's disease under different movement feedback conditions. *Behavioural Brain Research*, *159*, 127–133. DOI:10.1016/j.bbr.2004.10.009

Tailby, R., & Haslam, C. (2003). An investigation of errorless learning in memory-impaired patients: improving the technique and clarifying theory. *Neuropsychologia*, *41,* 1230–1240. DOI: 10.1016/S0028-3932(03)00036-8

Talland, G.A. (1965). Deranged memory: A psychonomic study of the amnesic syndrome. New York: Academic Press

Thivierge, S., Simard, M., Jean, L., & Grandmaison, E. (2008). Errorless learning and spaced retrieval techniques to relearn instrumental activities of daily living in mild Alzheimer's disease: A case report study. *Journal of Neuropsychiatric Disease and Treatment*, *4*, 987-999. DOI: 10.2147/NDT.S3684

Thomson, A.D. (2000). Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol and Alcoholism Supplement*, *35*, 2-7.

Thomson A.D., Cook C.H., Touquet R., & Henry J.A. (2002). The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. *Alcohol and Alcoholism, 37*, 513-521. DOI: 10.1093/alcalc/agh249

Thomson A.D., & Marshall E.J. (2006). The natural history of Wernicke's encephalopathy and Korsakoff's psychosis. *Alcohol and Alcoholism, 41*, 151-158. DOI: 10.1093/alcalc/agh249

Thomson, A.D., & Marshall, E.J. (2013). Time to act on the inadequate management of Wernicke's encephalopathy in the UK. *Alcohol and Alcoholism, 48*, 4-8. DOI: 10.1093/alcalc/ags111

Thöne A.I. (1996). Memory rehabilitation - recent developments and future directions. *Restorative Neurology and Neuroscience*, *9,* 125-140. DOI: 10.3233/RNN-1996-9301

Tombaugh, T.N.T.N (2004). Trail Making test A and B: Normative Data Stratified by Age and Education. *Archives of Clinical Neuropsychology 19*, 203–214. DOI: 10.1016/S0887-6177(03)00039-8

Uterwijk, J. (2000). *WAIS–III Technical manual (in Dutch)*. Lisse, The Netherlands: Swets & Zeitlinger.

Van Asselen, M., Kessels, R.P.C., Wester, A. &, Postma, A. (2005). Spatial working memory and contextual cueing in patients with Korsakoff amnesia. *Journal of Clinical and Experimental Neuropsychology, 27*, 645–655. DOI: 10.1081/13803390490919281

Van Asselen, Fritschy, E., & Postma, A. (2006). The influence of intentional and incidental learning on acquiring spatial knowledge during navigation. *Psychological Research, 70*, 151-156. DOI: 10.1007/s00426-004-0199-0

Van Asselen, M., Kessels, R.P.C., Neggers, S.F.W., Kappele, L.J., Frijns, C.J.M., & Postma, A. (2006). Brain areas involved in spatial working memory. *Neuropsychologia, 44,* 1185-1194. DOI: 10.1016/j.neuropsychologia.2005.10.005

Van Asselen, M., Kessels, R.P.C., Kappelle, L.J., & Postma A. (2008). Categorical and coordinate spatial representations within object-location memory. *Cortex*, *44*, 249-256. DOI: 10.1016/j.cortex.2006.05.005

Van Asselen, M., Almeida, I., Andre, R., Januário, C., Gonçalves, A.F. & Castelo-Branco, M. (2009). The role of the basal ganglia in implicit contextual learning: A study of Parkinson's disease. *Neuropsychologia, 47*, 1269-1273. DOI: 10.1016/j.neuropsychologia.2009.01.008.

Van Asselen M., Júlio F., Almeida I., Januário C., Bobrowicz Campos E., Freire A. & Castelo-Branco M. (2010). Basal ganglia dysfunction caused by Huntington's disease impairs nonmotor visual learning. *poster presented on the FENS Forum 2010, 07/05/10 - FENS Abstr., vol.5, 114.50, 2010*.

van Asselen, M., Almeida, I., Júlio, F., Januário, C., Campos, E.B., Simões, M., & Castelo-Branco, M. (2012). Implicit Contextual Learning in Prodromal and Early Stage Huntington's Disease Patients. *Journal of the International Neuropsychological Society, 18*, 689-696. DOI: 10.1017/S1355617712000288

Van Balen, H.G.G., & Wimmers, M.F.H.G. (1992). *Rivermead Behavioural Memory Test. Normeringsgegevens*. Nijmegen: Katholieke Universiteit Nijmegen.

Van Damme, I., & d'Ydewalle, G. (2008). Elaborative processing in the Korsakoff syndrome: context versus habit. *Brain and Cognition*, *67*, 212–224. DOI: 10.1016/j.bandc.2008.01.004

Van Der Elst W., Van Boxtel, M.P.J., Van Breukelen G.J.P., & Jolles J. (2005). Rey's verbal learning test: Normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11,* 290–302. DOI:10.1017/S1355617705050344

Van der Linden, M., Meulemans, T., & Lorrain, D. (1994). Acquistion of new concepts by two amnesic patients. *Cortex, 30*, 305–317. DOI:10.1016/S0010-9452(13)80201-8

van der Ham I.J., van Zandvoort M.J., Meilinger T., Bosch S.E., Kant N., & Postma A. (2010). Spatial and temporal aspects of navigation in two neurological patients. *Neuroreport, 14*, 685-689. DOI: 10.1097/WNR.0b013e32833aea78

Van der Stigchel, S., Reichenbach, R.C.L., Wester, A.J., & Nijboer, T.C.W. (2012). Antisaccade performance in Korsakoff patients reveals deficits in oculomotor inhibition. *Journal of Clinical and Experimental Neuropsychology*, *34*, 876–886. DOI: 10.1080/13803395.2012.692771

Van Geldorp, B., Bergmann, H. C., Robertson, J., Wester, A. J., & Kessels, R. P. C. (2012). The interaction of working memory performance and episodic memory formation in patients with Korsakoff's amnesia. *Brain Research, 1433*, 98–103. DOI: 10.1016/j.brainres.2011.11.036

van Hoof, J., Aarts, M.P.J., Rense, C.G., Schoutens, A.M.C. (2009). Ambient bright light in dementia: Effects on behaviour and circadian rhythmicity. *Building and Environment*, *44*, 146-155. DOI: 10.1016/j.buildenv.2008.02.005

Van Oort, R., & Kessels, R.P.C. (2009). Executive dysfunction in Korsakoff's syndrome: Time to revise the DSM criteria for alcohol-induced persisting amnestic disorder? *International Journal of Psychiatry in Clinical Practice*, *13*, 78-81. DOI: 10.1080/13651500802308290

Van Tilborg, I.A.D.A., Kessels, R.P.C., Kruijt, P., Wester, A.J., & Hulstijn, W. (2011). Spatial and nonspatial implicit motor learning in Korsakoff's amnesia: Evidence for selective deficits. *Experimental Brain Research*, *214*, 427-435. Doi: 10.1007/s00221-011-2841-6

Verfaellie, M., Milberg W.P., Cermak L.S., & Letourneau L.L. (1992). Priming of spatial configurations in alcoholic Korsakoff's amnesia. *Brain and Cognition, 18*, 34–45. DOI: 10.1016/0278-2626(92)90109-Y

Verfaellie, M., Gabrieli, J.D., Vaidya, C.J., Croce, P., & Reminger, S.L. (1996). Implicit memory for pictures in amnesia: Role of etiology and priming task. *Neuropsychology*, *10*, 517–528. DOI: 10.1037/0894-4105.10.4.517

Verhage F. (1964). *Intelligence and age* (in Dutch). Assen, The Netherlands: van Gorcum.

Von Stülpnagel, R., & Steffens, M.C. (2013). Active route learning in virtual environments: Disentangling movement control from intention, instruction specificity, and navigation control. *Psychological Research 77*, 555-574. DOI: 10.1007/s00426-012-0451-y

Waller, D., & Richardson, A.R. (2008). Correcting distance estimates by interacting with immersive virtual environments: effects of task and available sensory information. *Experimental Psychology: Applied,* 14, 61-72. DOI: 10.1037/1076-898X.14.1.61

Wang, D., Hazell, A.S. (2010). Microglial activation is a major contributor to neurologic dysfunction in thiamine deficiency. *Biochemical and Biophysical Research Communications, 402*, 123-128. DOI: 10.1016/j.bbrc.2010.09.128

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale – Third Edition*. San Antonio, TX: Psychological Corporation.

Welch, L.W., Cunningham, A.T., Eckardt, M.J., Martin, P.R. (1997). Fine Motor Speed Deficits in Alcoholic Korsakoff's Syndrome. *Alcoholism: Clinical and Experimental Research, 21*, 134-139. DOI: 10.1111/j.1530-0277.1997.tb03741.x

Wernicke, C. (1881). Die acute haemorrhagische poliencephalitis superior. Translated by Brody, I.A. , & Wilkins, R.H. (1968). Acute Hemorrhagic Superior Polioencephalitis. *Archives of Neurology*, 19, 228-232. DOI:

Wester, A.J., Westhoff, J., Kessels, R.P.C., & Egger, J.I.M. (2013). The Montreal Cognitive Assessment (MoCa) as a measure of severity of amnesia in patients with alcohol-related cognitive impairments and Korsakoff syndrome. *Clinical Neuropsychiatry, 10*, 134-141.

Wijnia, J.W., & Oudman, E. (2013). Biomarkers of delirium as a clue to diagnosis and pathogenesis of Wernicke-Korsakoff syndrome. *European Journal of Neurology*, 12, 1531-1538. DOI: 10.1111/ene.12217

Wijnia, J.W., & Goossensen, A. (2010). Cerebellar neurocognition and Korsakoff's syndrome: An hypothesis. *Medical Hypotheses*, *75*, 266-268. DOI: 10.1016/j.mehy.2010.02.035

Wilson B., Cockburn J., & Baddeley A. (1985). *The Rivermead Behavioural Memory Test.* Reading, England: Thames Valley Test Company

Wilson, B.A., Baddeley, A., & Evans, J. (1994). Errorless learning in the rehabilitation of memory impaired people. *Neuropsychological Rehabilitation*, *4*, 307-326. Doi: 10.1080/09602019408401463

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H., & Evans, J. J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome (BADS)*. Bury St Edmunds, U.K.: Thames Valley Test Company.

Wilson B.A. (2008). Neuropsychological Rehabilitation. *Annual Review of Clinical Psychology*, *4*, 141-162. DOI:10.1146/annurev.clinpsy.4.022007.141212

Wilson, B.A. (2009). *Memory rehabilitation: integrating theory and practice*. The Guilford Press, New York, United States of America.

Wolf, R.C., Vasic, N., Schönfeldt-Lecuona, C., Ecker, D., & Landwehrmeyer, G.B. (2009). Cortical dysfunction in patients with Huntington's disease during working memory performance. *Human Brain Mapping, 30*, 327-339. DOI: 10.1002/hbm.20502.

Wood, F., Ebert, V., Kinsbourne, M. (1982). The episodic-semantic distinction in memory and amnesia: Clinical and experimental observations. In L.S. Cermak (Ed.) Human memory and amnesia. Hillsdale, Erlbaum.

Zahr N.M., Kaufman K.L., & Harper C.G. (2011). Clinical and pathological features of alcohol related brain damage. *Nature Review Neurology, 7*, 284-294. DOI:10.1038/nrneurol.2011.42

Publications

Oudman, E., Van der Stigchel S., Wester A.J., Kessels R.P.C., & Postma A. (2011). Intact memory for implicit contextual information in Korsakoff's amnesia. *Neuropsychologia*, *49*, 2848-2855. DOI:10.1016/j.neuropsychologia.2011.06.010

Bossong, M.G., Jansma, J.M., van Hell, H.H., Jager, G., Oudman, E., Saliasi, E., Kahn, R.S., Ramsey, N.F. (2012). Effects of δ9-tetrahydrocannabinol on human working memory function. *Biological Psychiatry, 71*, 639-699. DOI: 10.1016/j.biopsych.2012.01.008.

Oudman E. (2012). Is electroconvulsive therapy (ECT) effective and safe for treatment of depression in dementia? A short review. *Journal of ECT, 28*, 34-38. DOI: 10.1097/YCT.0b013e31823a0f5a.

Oudman, E., & Zwart, E. (2012). Quality of life of patients with Korsakoff's syndrome and patients with dementia: a cross-sectional study. *Journal of the American Medical Directors Association*, *13*, 778-781. DOI: 10.1016/j.jamda.2012.08.003

Oudman, E. (2012). Electroconvulsietherapie (ECT) als behandeling voor depressie bij dementerenden? *Neuropraxis, 16*, 116-120. DOI: 10.1007/s12474-012-0020-6

Oudman E., Nijboer T.C.W., Postma A., Wijnia J.W., Kerklaan S., Lindsen K., & Van der Stigchel S. (2013). Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: A comparison of trial and error and errorless learning. *Neuropsychological Rehabilitation, 23,* 888-913. DOI: 10.1080/09602011.2013.835738

Wijnia, J.W., & Oudman, E. (2013). Biomarkers of delirium as a clue to diagnosis and pathogenesis of Wernicke-Korsakoff syndrome. *European Journal of Neurology*, 12, 1531-1538. DOI: 10.1111/ene.12217

Oudman, E., & Wijnia, J.W. (2014). BNF Recommendations for the Treatment of Wernicke's Encephalopathy: Lost in Translation? *Alcohol and Alcoholism*, *49,* 118. DOI: 10.1093/alcalc/agt179

Oudman, E., Van der Stigchel, S., Postma, A., Wijnia, J.W., Nijboer, T.C.W. (2014). A Case of Chronic Wernicke's Encephalopathy: A Neuropsychological Study. *Frontiers in Psychiatry, 5*, DOI: 10.3389/fpsyt.2014.00059

Oudman, E., Wijnia, J.W. (2014). Evolution of quality of life in Korsakoff's syndrome. *International Psychogeriatrics*, *26*, 2073-2079. doi: 10.1017/S1041610214001719

Oudman E, Wijnia JW. (2014). Korsakoff's syndrome is preventable. *American Journal of Emergency Medicine*, *32*, 1417-1418. doi: 10.1016/j.ajem.2014.08.017.

Oudman, E., Postma, A., Van der Stigchel, S., Appelhof, B., Wijnia, J.W., Nijboer, T.C.W. (2014). The Montreal Cognitive Assessment (MoCA) is Superior to the Mini-Mental State Examination (MMSE) in Detection of Korsakoff's Syndrome. *The Clinical Neuropsychologist*, *28*, 1123-1132. DOI: 10.1080/13854046.2014.960005

Oudman, E., Van der Stigchel, S., Nijboer, T.C.W., Wijnia, J.W., Seekles, M.L., Postma, A. Route learning in Korsakoff's syndrome: residual acquisition of spatial memory despite profound amnesia. *Journal of Neuropsychology*, in press. DOI: 10.1111/jnp.12058

Wijnia, J.W., Oudman, E., Bresser, E.L., Gerridzen, I.J., van de Wiel, A., Beuman, C., Mulder, C.L. (2014). Early Diagnosis of Mental and Mobility Changes in Wernicke-Korsakoff Syndrome. *Cognitive and Behavioral Neurology*, *27*, 215-221. DOI: 10.1097/WNN.0000000000000041

Oudman, E., Postma, A., Van der Stigchel, S., Appelhof, B., Wijnia, J.W., Nijboer, T.C.W. (2015). De MoCA en MMSE als screeningsinstrumenten voor alcoholgerelateerde cognitieve stoornissen en het syndroom van Korsakov. *Neuropraxis*, *2*, 39-43. DOI: 10.1007/s12474-015-0078-z

Oudman, E., Nijboer, T.C.W., Postma, A., Wijnia, J.W., Van der Stigchel, S. (2015). Procedural learning and memory rehabilitation in Korsakoff's syndrome - a review of the literature. *Neuropsychology Review*, *25*, 134-148.

Nederlandse samenvatting

Achtergrond

De afgelopen jaren ben ik in mijn werk als psycholoog veel langdurig alcoholisten tegengekomen in een observatie- en verblijfscentrum voor mensen met het syndroom van Korsakov. De meerderheid van deze mensen was van het mannelijk geslacht, 50 tot 60 jaar oud, met een verleden dat gekenmerkt werd door sociaal isolement, werkloosheid, zelfverwaarlozing en vaak agressie ten gevolge van intensief alcoholgebruik. Veel van deze alcoholisten hadden al de diagnose "Het syndroom van Korsakov" (hierna: Korsakov) of kregen deze diagnose tijdens hun verblijf in het centrum.

Korsakov is vernoemd naar de Russische arts Sergej Korsakov (1854-1900). Hij omschreef de problemen die hij zag bij een deel van de alcoholisten die hij tegen kwam in zijn praktijk. In de klinische literatuur wordt Korsakov gezien als een ernstige, blijvende aandoening met selectieve problemen in het cognitieve functioneren die niet progressief achteruit gaan over tijd. Bij mensen met Korsakov staan de problemen in het onthouden van *declaratieve informatie* na het ontstaan van de aandoening centraal. Zo onthoudt een persoon met Korsakov vaak niet meer waar hij is, wat hij daar doet en hoe lang hij daar is. Het overige cognitieve functioneren is relatief beter bewaard gebleven bij Korsakov. Zo hebben mensen met Korsakov vaak een intelligentieniveau dat vrijwel overeen komt met het niveau van functioneren voordat zij Korsakov kregen. In de praktijk kan dit betekenen dat iemand met Korsakov een gevatte grap maakt, maar vervolgens de grap niet kan onthouden en deze voortdurend herhaalt. Of het kan betekenen dat iemand met Korsakov een bezoeker attendeert op zijn loszittende veter, maar vervolgens zich wel herhaaldelijk blijft voorstellen, omdat hij niet onthouden heeft dat hij de persoon eerder heeft gezien.

De recentelijk overleden neuroloog Oliver Sacks vertelt in zijn boek "De man die zijn vrouw voor een hoed hield" uit 1985 het verhaal "De verloren zeeman". Dit verhaal gaat over één van de mensen met Korsakov die hij zag op zijn afdeling. Jimmie, de man met Korsakov, was soldaat geweest in de Tweede Wereldoorlog. In zijn geheugen leefde Jimmie nog steeds in 1945, terwijl het inmiddels in de jaren '70 was. Jimmie kon gebeurtenissen uit de oorlog en de namen van de vliegtuigen tot 1945 goed navertellen en benoemde in de gesprekken met Oliver Sacks dat hij feest vierde , omdat de oorlog nu voorbij was. Het verhaal van Oliver Sacks geeft een goed inzicht van de alledaagse problemen in de omgang met Korsakov en laat daarnaast zien hoe fors de geheugenproblemen kunnen zijn bij Korsakov.

Waar gaat dit proefschrift over en waarom gaat het daar over?

In dit proefschrift staan drie thema's centraal. Het eerste thema is hoe de diagnostiek van Korsakov verbeterd zou kunnen worden. Dit thema is relevant, omdat er nog steeds veel mensen met Korsakov de verkeerde diagnose krijgen. Soms wordt Korsakov bijvoorbeeld foutief aangezien als een vorm van progressieve dementie en soms wordt de diagnose te vroeg gesteld. Het tweede thema is hoe mensen met Korsakov ondanks hun ernstige geheugenproblemen toch kunnen leren. Dit thema is eveneens cruciaal, omdat er nog maar weinig bekend is over wat mensen met Korsakov nog wel kunnen onthouden, ondanks hun ernstige geheugenproblemen. Het derde thema is hoe de intacte vormen van geheugen en leren ingezet kunnen worden in geheugenrevalidatie. Dit thema is van fundamenteel belang, omdat bij Korsakov de autonomie beperkt is ten gevolge van de cognitieve problematiek en revalidatie zou kunnen leiden tot vergroting van de autonomie.

Thema 1: Wat is de oorzaak van Korsakov en hoe wordt de diagnose gesteld?

Een belangrijke vitamine voor het omzetten van suikers in energie in de hersenen is vitamine B1. Vitamine B1 zit in veel verschillende soorten voeding, zoals graanproducten, melk, zilvervliesrijst en aardappels. De inname, opslag en verwerking van deze vitamine is bij alcoholisten verminderd, waardoor zij een sterk verhoogd risico hebben op tekorten. Als deze tekorten oplopen, kunnen ze leiden tot Wernicke Encefalopathie. Dit is een acuut, levensbedreigend neurologisch ziektebeeld waarbij verwardheid, motorische problemen en algehele malaise centraal staan. Wanneer een patiënt met deze levensbedreigende ziekte snel behandeld wordt met hooggedoseerde vitamine B1 injecties, dan kunnen de problemen (vrijwel) geheel herstellen. In het tweede hoofdstuk van dit proefschrift wordt een casus omschreven van een vrouw met Wernicke Encefalopathie. In plaats van tijdige behandeling kreeg zij gedurende vijf dagen geen behandeling voor deze ziekte. De vrouw bleef de ernstige neurologische en psychiatrische problemen houden. In het artikel wordt omschreven dat het niet opmerken en behandelen van een acute Wernicke Encefalopathie kan leiden tot een chronische Wernicke Encefalopathie.

Als er sprake is van Wernicke Encefalopathie is een minimale periode van zes weken nodig voordat Korsakov formeel vastgesteld kan worden. Korsakov kan zich echter ook sluipenderwijs ontwikkelen, zonder een duidelijke Wernicke Encefalopathie. Voor het vaststellen van Korskakov is een uitgebreid neuropsychologisch onderzoek van belang, omdat dit een gedetailleerde analyse van de cognitieve problemen geeft, naast het in kaart brengen van de factoren die geleid hebben tot Korsakov. In de klinische praktijk worden vaak ook cognitieve screeningsinstrumenten ingezet om een snelle indruk te krijgen van het cognitieve functioneren. Hoofdstuk 3 van dit proefschrift bekijkt of cognitieve screeningsinstrumenten toepasbaar zijn bij het opmerken van Korsakov. De meest toegepaste instrumenten zijn de Mini-Mental State Examination (MMSE) en de Montreal Cognitive Assessment (MoCA). Het onderzoek laat zien dat hoewel beide instrumenten goede eigenschappen hebben om Korsakov op te merken, de MoCA beter is.

Hoofdstuk 4 gaat in op de periode na het diagnosticeren van Korsakov. Een gedeelte van de mensen met deze aandoening kan onder begeleiding nog zelfstandig wonen, maar een ander gedeelte is afhankelijk van langdurige zorg. In dit hoofdstuk staat de vraag centraal of de kwaliteit van leven van mensen met Korsakov vergelijkbaar is met die van mensen met vormen van dementie in een verpleeghuissetting. Kwaliteit van leven is een term die vaak gebruikt wordt met betrekking tot het welzijn van mensen. Meestal wordt dit vastgesteld middels vragenlijsten of observatieinstrumenten. Uit dit onderzoek komt naar voren dat mensen met Korsakov andere behoeften en wensen hebben dan mensen met dementie, ook na correctie voor leeftijdsverschillen en instellingsverschillen. Een belangrijke conclusie uit dit onderzoek is daarom dat mensen met Korsakov beter gespecialiseerde langdurige zorg kunnen krijgen dan reguliere psychogeriatrische zorg voor mensen met dementie.

Thema 2: Wat onthouden mensen met Korsakov nog wel?

In het tweede deel van dit proefschift wordt gekeken naar verschillende vormen van contextueel leren. Een belangrijke vorm van contextueel leren is het ruimtelijk leren. Dit type leren is relevant om bijvoorbeeld te onthouden waar je fiets staat en om van A naar B te komen, zonder dat je iedere keer volledig de weg kwijt raakt. Voor contextueel leren maak je gebruik van zowel het *declaratieve* als *niet-declaratieve geheugen*.

Het declaratieve geheugen is het geheugen voor het onthouden van feitelijke informatie en persoonlijk relevante informatie (onthouden van “wat”-informatie). In dit type geheugen wordt bijvoorbeeld de informatie opgeslagen over wat je gisteren gegeten hebt en wat de hoofdstad van Frankrijk is. Bij Korsakov zijn er forse problemen ten aanzien van dit type geheugen. Het is nog niet bekend hoe goed het niet-declaratieve geheugen functioneert bij mensen met Korsakov. Het niet-declaratieve geheugen is het geheugen voor het onthouden van vaardigheden en verbanden (onthouden van “hoe”-informatie). In dit type geheugen wordt bijvoorbeeld opgeslagen hoe je een auto moet besturen of hoe je fiets.

Bij Korsakov zijn er ernstige problemen in dit proces, zoals we weten uit de literatuur en bij het zien van deze mensen in de kliniek.

Hoofdstuk 5 van dit proefschrift gaat over verschillende vormen van ruimtelijk en verbaal geheugen bij Korsakov. Verbaal geheugen is het geheugen voor woorden, getallen en symbolen, terwijl ruimtelijk geheugen het geheugen is voor het onthouden van plaatsen en objecten in onze omgeving. In dit hoofdstuk wordt daarnaast een onderscheid gemaakt tussen verschillende processen van het geheugen. Wanneer mensen bijvoorbeeld iets zien of of lezen, wordt dit niet direct opgeslagen in het langetermijngeheugen. Eerst zal deze informatie beschikbaar zijn voor het werkgeheugen waar het beschikbaar is om er gesprekken over te voeren, het te koppelen aan eerdere informatie uit het langetermijngeheugen en op die manier de informatie te bewerkenen na te denken over deze informatie. Het werkgeheugen is beperkt in de hoeveelheid informatie die er in opgeslagen kan worden. Het langetermijngeheugen is de langdurige opslag voor herinneringen. In dit hoofdstuk vinden we dat het ruimtelijke geheugen beter bewaard is gebleven dan het verbale geheugen. Deze relatieve sparingen zijn het sterkste aanwezig in de vroege processen (het werkgeheugen) ten opzichte van de latere processen (langetermijngeheugen). Omdat er sparingen waren in het ruimtelijke geheugen, is een aanbeveling uit het onderzoek om het ruimtelijke geheugen vaker in te zetten bij geheugenrevalidatie voor mensen met Korsakov. Dit kan bijvoorbeeld gedaan worden door de omgeving waar gerevalideerd wordt gelijk te houden over situaties. Mogelijk speelt in dit onderzoek ook het niet-declaratieve ruimtelijke leren een rol.

Hoofdstuk 6 gaat dieper in op het niet-declaratieve ruimtelijke leren. Een voorbeeld van dit niet-declaratieve leren is dat je zonder nadenken naar je fiets loopt bij het station, als die fiets vaak op dezelfde plek neergezet is. In hoofdstuk 6 staat de vraag centraal of dit type geheugen bij mensen met het syndroom van Korsakov gespaard is gebleven in de vorm van impliciet contextueel leren. In de taak die omschreven staat in dit hoofdstuk, is het de bedoeling om een figuur te ontdekken tussen elf andere figuren. De helft van de opstellingen van de figuren wordt gedurende het experiment herhaald, terwijl de andere helft dit niet wordt. In het huidige onderzoek komt naar voren dat mensen met Korsakov in staat zijn om te profiteren van deze herhaling, wat suggereert dat het niet-declaratieve ruimtelijke leren nog goed is. Dus ook mensen met Korsakov zouden hun fiets zonder nadenken moeten kunnen terugvinden als die fiets vaak op dezelfde plaats is gezet. In de dagelijkse praktijk zien we dit bijvoorbeeld terug bij het hebben van vaste bewaarplekken voor sigaretten en aanstekers.

In hoofdstuk 7 gaat het over een wat meer complexe geheugenfunctie dan het impliciet ruimtelijke leren, namelijk het leren van routes. Zowel declaratieve als niet-declaratieve geheugenprocessen spelen een rol bij het leren van routes.

In dit onderzoek wordt gekeken wat mensen met Korsakov onthouden na het eenmalig zien en lopen van een korte route. Naar voren komt dat de prestaties op de meerderheid van de taken die betrekking hadden op het leren van routes bij mensen met Korsakov verminderd is. Wanneer de prestaties vergeleken werden met kansniveau (hoe goed iemand het zou doen die niet weet wat de taak is), presteren de Korsakovs op de meerderheid van de taken beter. Dit suggereert dat er ergens nog de mogelijkheid is om routes op te slaan, zij het op een veel lager niveau dan bij gezonde mensen.

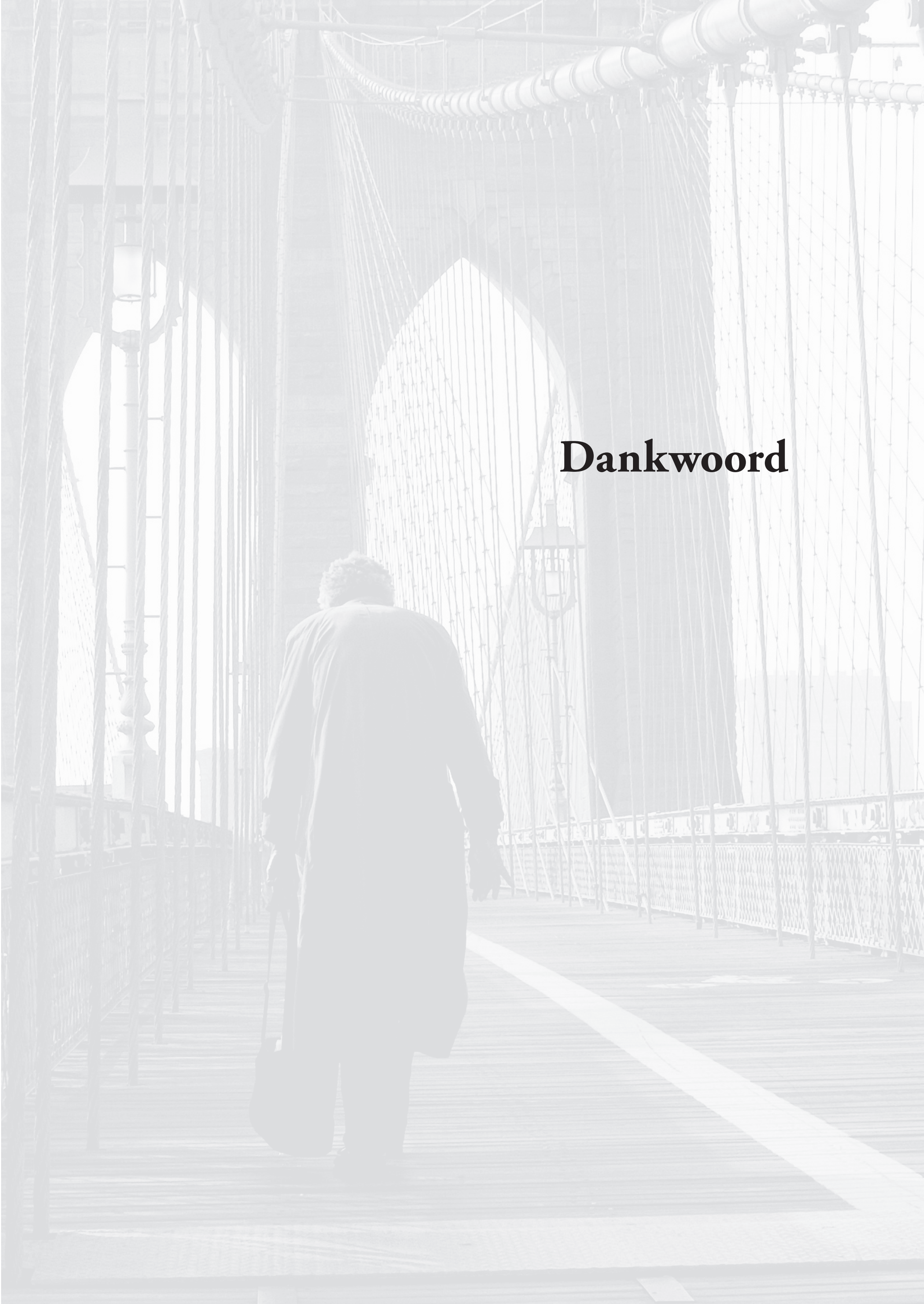
Thema 3: Hoe kan het vermogen tot leren ingezet worden voor revalidatie van geheugenfuncties?

Een centraal probleem in de langdurige zorg voor mensen met Korsakov is het vraagstuk hoe zij optimaal gerevalideerd kunnen worden, zodat hun autonomie vergroot kan worden. Zoals omschreven in het tweede deel van dit proefschrift hebben mensen met Korsakov nog enig vermogen om te leren, ondanks hun ernstige beperkingen in het geheugen. De sparingen in het geheugen zijn voornamelijk aanwezig in het procedurele leren ("hoe"), terwijl het declaratieve geheugen ("wat") ernstig is aangedaan. Voor revalidatie van geheugenfuncties zijn de sparingen in het geheugen relevant, omdat ze kunnen compenseren voor het aangetaste geheugen.

Hoofdstuk 7 is een overzichtsartikel van de literatuur aangaande het procedurele leren en geheugen. Een belangrijke conclusie van het overzichtsartikel is dat mensen met Korsakov nog redelijk in staat zijn om procedures en vaardigheden te leren, ondanks hun ernstige declaratieve geheugenproblemen. In veel taken behalen de mensen met Korsakov niet het maximaal haalbare niveau, maar laten ze wel verbetering zien door training. In het onderzoek worden enkele aanbevelingen gedaan voor het opzetten van revalidatieprogramma's voor mensen met Korsakov. Een suggestie is het vereenvoudigen van taken, zodat de taak gemakkelijker opgeslagen kan worden in het procedurele geheugen. Daarnaast is het voor mensen met Korsakov relevant om feedback te krijgen tijdens de taak. Dit zorgt voor verbetering van het leren. Het inzetten van (digitale) hulpmiddelen wordt steeds belangrijker volgens de huidige literatuur. Recentelijk wordt er in de klinische literatuur ook steeds vaker gebruik gemaakt van foutloos leren. Dit is een sterk structurerende manier van aanleren, waarbij fouten tijdens het leerproces voorkomen worden om het geheugen te ondersteunen. Deze nieuwe techniek lijkt bijzonder voor mensen met Korsakov, omdat omdat deze techniek een beroep lijkt te doen op het relatief beter bewaard gebleven procedurele geheugen.

In het laatste hoofdstuk van deel drie staat foutloos leren centraal bij het aanleren van het alledaagse vaardigheden. Het doel van dit onderzoek is om te onderzoeken of foutloos leren een effectieve methode is voor het (opnieuw) aanleren van het doen van de was. In dit onderzoek vergeleken we de prestaties van acht mensen met Korsakov, die middels foutloos leren leerden om een wasmachine te bedienen, met de prestaties van acht mensen met Korsakov, die met vallen en opstaan (trial-and-error leren) leerden om een wasmachine te bedienen. In de laatste groep mochten mensen met Korsakov dus wel fouten maken tijdens het leerproces, terwijl deze in de eerste groep voorkomen werden. Beide interventies resulteerden in vergelijkbare verbetering over acht leersessies. In een andere omgeving, bij het doen van de was in een andere wasmachine, was de prestatie nog steeds verbeterd. Na vier weken waarin de mensen met het syndroom van Korsakov de was niet deden, bleef de prestatie bij de groep die middels foutloos leren had geleerd verhoogd; terwijl bij trial-and-error leren dit niet het geval was. De resultaten van dit onderzoek tonen aan dat het aanleren en het behouden van een alledaagse vaardigheid mogelijk is bij mensen met het syndroom van Korsakov. In de alledaagse zorg kan het toepassen van foutloos leren de zelfstandigheid van mensen met cognitieve problemen verhogen en is het effectiever op de langere termijn.

Kortom, zoals de onderzoeken in dit proefschrift laten zien kunnen mensen met Korsakov impliciet en procedureel leren. Dit leervermogen is relevant voor het uitvoeren van alledaagse handelingen en draagt op deze manier bij aan het vergroten van de autonomie . Idealiter wordt er daarom op twee momenten behandeling gegeven: in de acute fase middels vitamine B1 injecties om mensen te beschermen tegen het syndroom van Korsakov, in de chronische fase middels cognitieve revalidatie en het optimaal benutten van het residuele geheugen. Het inzetten van deze soorten behandeling kan zo bijdragen aan het reconstrueren van cognitie in het syndroom van Korsakov.



Dankwoord

Om te beginnen wil ik mijn promotor Prof. Dr. Albert Postma en co-promotoren Dr. Stefan Van der Stigchel en Dr. Tanja Nijboer bedanken voor het creeëren van deze promotieplek en het bij nacht en ontij begeleiden van het proces naar deze promotie.

Albert, ik had vermoedelijk nu niet met mensen met Korsakov gewerkt, als jij in 2009 niet gewezen had op een idee voor een thesisproject bij het Vincent van Gogh Instituut in Venray (nu hoofdstuk 6 van dit proefschrift). Ook heb je het vertrouwen gehad dat het toch nog wat zou worden met mijn onderzoekscarrière, ondanks mijn klinische ambities. Hiervoor ben ik je de afgelopen vier jaar meestal dankbaar geweest. Bedankt ook voor het continu zien van mogelijkheden, het hebben van geduld en het opgewekt blijven ongeacht de omstandigheid.

Stefan, fijn dat je aan dit (toch wel behoorlijk neuropsychologie-)proefschrift hebt willen meewerken en mij hebt geholpen een onderzoeker te worden. Bedankt voor je waanzinnige enthousiasme, de kunst om mensen aan het denken te blijven zetten en je vermogen om steeds te blijven motiveren.

Tanja, jij bent er bijgekomen toen het project een promotietraject werd. Met je uitgebreide ervaring in het patiëntenonderzoek maakte je het drietal compleet. Ik wil je bedanken voor je scherpe blik tijdens het opzetten en uitvoeren van de onderzoeken uit dit proefschrift, je humor en je liefde voor de patiënten.

Albert, Stefan en Tanja, bedankt voor jullie toegankelijkheid en vrijheid gedurende het hele project en de vaak geestige bijeenkomsten die we hadden.

Prof. dr. Iris Engelhard, Dr. Martine van Zandvoort, Prof. dr. Luciano Fasotti, Prof. dr. Edward de Haan en Prof. dr. Martijn Meeter, ik wil u bedanken voor het lezen en het goedkeuren van mijn manuscript als beoordelingscommissie.

Middels deze weg wil ik de stichting Topcare bedanken voor het opzetten van een Korsakov-lijn binnen de specialistische verpleeghuiszorg. Het geeft deze doelgroep de erkenning die ze verdienen en zal uiteindelijk leiden tot verbetering van de zorg voor deze doelgroep.

Ik wil de Lelie Zorggroep en Korsakovcentrum Slingedael bedanken voor de mogelijkheden en tijd die ik nu al heb gekregen om onderzoek te verrichten en te promoveren. Het doen van onderzoek is nog steeds uniek binnen de Verpleeg- en Verzorgingshuissector en daarom is het ontzettend mooi om er aan bij te kunnen dragen. Een heel aantal mensen wil ik in het bijzonder noemen:

Lidy Bezemer, als manager van het Korsakovcentrum Slingedael heb je er voor gezorgd dat onderzoek nu echt een plek krijgt in Slingedael. Goed dat dit nu ook beloond is met het Topcare predicaat.

Gerrit Nieuwenhuis, het opzetten van een 'psychologen-lijn' in het onderzoek heeft fundamenteel bijgedragen aan mijn promotie en de reeds vele onderzoeken naar Korsakov en cognitie die we hebben kunnen uitvoeren. Ik waardeer je drive voor het verbeteren van de omstandigheden van mensen die het niet voor het uitkiezen hebben en je grote kennis over de zorg voor zorgwekkende zorgmijders.

Ik wil het bestuur van de Lelie Zorggroep bedanken voor het in mij gestelde vertrouwen in deze kans om wetenschappelijk onderzoek en klinische praktijk nader bij elkaar te brengen. In het bijzonder bedank ik Johan van der Ham, Frans Knuit, Peter Muis en Helena Smit voor hun inspanningen om dit promotietraject tot een succes te maken.

Dr. Jan Wijnia, als ex-medepromovendus en ervaren arts verdien je een aparte paragraaf in deze tekst. Ik heb gedurende het project veel aan je gehad en veel van je geleerd. Je analytische blik heeft geholpen om alert te blijven op de patronen, een eigenschap die als onderzoeker steeds van pas komt.

Ik wil hier stilstaan bij mijn collega-psychologen van Slingedael: Jackelien Hollebrandse, Marloes Olivier, Angela Lau en Jeanine Noeverman: dank jullie wel voor het aanhoren van mijn wetenschappelijke verhalen en het blijven supporten door de tijd. We hebben een goed team dat elkaar steeds kan aanvullen. Jullie maken met je enthousiasme het fijn om weer op Slingedael te zijn. Ook ben ik ontzettend trots als ik zie wat voor geweldige ideeën er de afgelopen jaren ontstaan zijn om de Korsakovzorg en behandeling te verbeteren.

Lenie Vermeer, dankjewel voor de enorme energie die je als mijn werkbegeleider en praktijkopleider voor de GZ-opleider weet over te brengen.

Ook de andere psychologen die werkzaam zijn voor Lelie Zorggroep WZW wil ik bedanken: Judith Dorrestijn, Wouter van Sabben; Charlotte den Uijl; Rianne Herrebout; Melanie de Weger en Caroline Verpoort, bedankt.

Bedankt OC: Albert, Elles, Floor, Jan en Mirjam

Sandra Kerklaan, Karen Lindsen en Esther den Haan, ik blijf het leuk vinden om te zien hoe foutloos leren kan bijdragen aan het aanleren van vaardigheden bij onze bewoners en het activeren van zorgmedewerkers. Jullie enthousiasme voor deze verbetering maakt niks onmogelijk. Ik hoorde laatst dat ons wasmachine-onderzoek het tot de V.S. heeft geschopt in presentaties over lerend vermogen.

Kristien Bortels, hoera we hebben een boek gemaakt! Na het doctoreren (in het Vlaams?) is er vast ontzettend veel tijd gekomen voor heel veel nieuwe projecten.

Ik heb nog heel veel meer collega's op Slingedael en binnen de Lelie Zorggroep die hier nog niet apart genoemd zijn, beginnend bij de zorgmedewerkers die elke dag als clown-annex-therapeut de doelgroep zover proberen te krijgen om toch uit bed te komen, zich te wassen, aan te kleden, te eten en dingen te gaan doen. En natuurlijk de vele behandelaren en begeleiders die betrokken zijn bij het verbeteren van de omstandigheden van mensen met Korsakov. Bedankt allemaal voor jullie mentale support tijdens het schrijven van dit proefschrift en jullie inzet om de situatie van de mensen met Korsakov te verbeteren. Of zoals een stagiair eens zei: "Het valt mij op dat jullie zo ontzettend enthousiast zijn, dat zie je haast niet meer". Laten we hopen dat ze inmiddels wel meer enthousiasme heeft gezien.

Uit Slingedael wil ik tot slot de bewoners bedanken. "Erik, je bent helemaal doorgeleerd. Dan gaat het helemaal niet goed met je".

Graag wil ik iedereen op de Universiteit Utrecht, afdeling Psychologische Functieleer bedanken. Ondanks mijn korte en ook versnipperde aanwezigheden vond ik het leuk om jullie in de koffieruimte, of op andere plekken in de hal, tegen het lijf te lopen.

In het bijzonder ook aandacht voor Nathan en Rudmer. Vaak en intensief denk ik terug aan het donkere hok op de 17^{e} etage alwaar wij The Journal of the European Mickey Mouse oprichtten. Inhoudelijk snap ik nog steeds niet heel veel van racemodellen en heatmaps, ondanks jullie vele wijze lessen. Toch voel ik me een echte wetenschapper. Ook mijn huidige roomies wil ik bedanken: Carla, Irene en Kim: leuk om af en toe te horen wat er in dat ziekenhuis allemaal gaande is. Neeltje, tof om te horen hoe ook bij jullie foutloos leren toegepast is. Jim en Surya, bedankt voor de lunches met bijzondere stellingen en wetenswaardigheden over de 20e en 21e eeuw. Sjoerd, je enthousiasme voor fundamenteel wetenschappelijk onderzoek heeft me, toen we nog cognitive neuroscience deden in de oertijd, gefascineerd. Ondanks dat we totaal iets anders zijn gaan doen is het leuk te horen hoe het ermee staat. Anouk, Martijn, Jasper, Haike, Alyanne, Miranda, Manasa et al. : bedankt.

Ik wil hier mensen bedanken die hebben bijgedragen aan de hoofdstukken uit dit proefschrift. Zonder de hulp van Britt en Maaike waren de hoofstukken 3 en 7 van dit proefschrift niet zo goed geworden als ze nu zijn. Sterker nog, waarschijnlijk waren ze er helemaal niet geweest. Bedankt voor het volgen van een thesisproject vanuit de Universiteit Utrecht in samenwerking met Slingedael. Ik had Arie Wester graag persoonlijk willen bedanken voor de tijd in Venray, maar zijn plotselinge overlijden heeft dit helaas onmogelijk gemaakt. Prof. dr. Roy Kessels, bedankt voor jouw scherpe analyses en het op weg helpen van mij in Venray. Bedankt ook voor je rijke onderzoekscarrière aangaande Korsakov en de vele andere patiëntengroepen. Elles Zwart, bedankt voor de samenwerking op het Qualidem-project en de tijd dat je als GZ-psycholoog bij Slingedael werkte. Inge van Stokkom bedankt voor het ordenen van de gegevens uit het ECD voor het Qualidem-project.

Dankjewel paranimfen Bertus Veurink en Theo Zielman. Jullie zijn ook bijzonder goede onderzoekers op het gebied van golfstromen, optiehandel, crematoria en historische hekwerken. Fijn dat jullie deze nobele klus op je willen nemen. Ook bij jullie promoties zal ik natuurlijk dankbaar dienst doen.

Schoonpa en ma (pem), Annet, Frits en kids; Erik en Susan, Ab en Jannette, Klaas, Agnes, Annelieke, Derk: jullie hebben geholpen om de boel in perspectief te blijven zien en jullie moeten daarbij alle staten die bij het maken van zo'n boek kunnen horen langs hebben zien komen. Fijn dat ik bij jullie terecht kon.

Dorienke, bij jou zijn is geweldig. Je maakt me gelukkig. Ik wil je bedanken voor de tijd die we samen hadden en die komen gaat.

Curriculum Vitae

Erik Oudman was born in Amersfoort on November 3th 1985. He graduated from high school at the Guido de Brès in Amersfoort in 2004. He obtained a Master of Science degree in Neuroscience & Cognition in 2010 and a Master of Science degree in Psychology in 2011, for which he performed an experimental study on implicit contextual learning in Korsakoff's syndrome. Since May 2011 he works as a psychologist in Korsakoff Center Slingedael, Rotterdam. His Phd project started in 2012 and finished in 2016. Next to his research, he follows an educational program to become a registered health-care psychologist.

Erik Oudman werd op 3 november 1985 geboren in Amersfoort. Hij slaagde voor het VWO examen op de Guido de Brès in Amersfoort in 2004. Hij behaalde een mastertitel in Neuroscience & Cognition in 2010 en een mastertitel psychologie in 2011, waarvoor hij onderzoek deed naar het impliciet ruimtelijk leren in patiënten met het syndroom van Korsakov. Hij werkt als psycholoog in Korsakovcentrum Slingedael vanaf mei 2011. Zijn promotieonderzoek begon in 2012 en eindigde in 2016. Op dit moment verricht hij onderzoek naast het volgen van de opleiding tot GZ-psycholoog.