EXECUTIVE FUNCTIONS IN PATIENTS WITH KORSAKOFF'S SYNDROME

Prevalence, severity, and association with neuropsychiatric symptoms

Wiltine Moerman

DONDERS SERIES

RADBOUD UNIVERSITY PRESS

Radboud Dissertation Series

EXECUTIVE FUNCTIONS IN PATIENTS WITH KORSAKOFF'S SYNDROME

Wiltine Moerman

The research presented in this thesis was supported by the Radboud University, Donders Institute for Brain, Cognition and Behaviour, Nijmegen in collaboration with Korsakoff Center of Expertise Markenhof, Atlant, Beekbergen. This work was partially supported by funding from the Topcare Foundation [Date: 2015-10-19]. The publication of this thesis was financially supported in part by the Korsakov Kenniscentrum (KKC; www.korsakovkenniscentrum.nl)

Executive functions in patients with Korsakoff's syndrome
Wiltine Moerman

Radboud Dissertation Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Jedi Noordegraaf
Printing: DPN Rikken/Pumbo

ISBN: 9789465151373
DOI: 10.54195/9789465151373
Free download at: https://doi.org/10.54195/9789465151373

RADBOUD
UNIVERSITY
PRESS

Executive functions in patients with Korsakoff's syndrome
Prevalence, severity, and association with neuropsychiatric symptoms

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 21 oktober 2025
om 12.30 uur precies

door

Willie Gertine van den Brink
geboren op 23 december 1988
te Ede

Promotoren:
Prof. dr. R. P. C. Kessels
Prof. dr. J. I. M. Egger

Copromotor:
Dr. L. van Aken

Manuscriptcommissie:
Prof. dr. J. Spijker
Prof. dr. A. Aleman (Maastricht University)
Prof. dr. D. L. Gerritsen

Contents

CHAPTER 1	General introduction	7
CHAPTER 2	Prevalence and severity of behavioural symptoms in patients with Korsakoff syndrome and other alcohol-related cognitive disorders: a systematic review *International Journal of Geriatric Psychiatry*, 32(3): 256–273. https://doi.org/10.1002/gps.4636	19
CHAPTER 3	Executive dysfunction in patients with Korsakoff's syndrome: a theory-driven approach *Alcohol & Alcoholism*, 54(1): 23–29. https://doi.org/10.1093/alcalc/agy078	51
CHAPTER 4	The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome *The Clinical Neuropsychologist*, 34(4): 740–754. https://doi.org/10.1080/13854046.2020.1738554	67
CHAPTER 5	the relation between behavioral, emotional and cognitive apathy and everyday executive dysfunction in alcoholic Korsakoff's syndrome *Archives of Clinical Psychiatry*, 48(3): 178–181. https://doi.org/10.15761/0101-60830000000301	83
CHAPTER 6	Is executive dysfunction associated with apathy in patients with alcoholic Korsakoff's syndrome?	93
CHAPTER 7	Summary and discussion	109
	References	124
	Research data management	138
	Nederlandse samenvatting	140
	Curriculum Vitae	152
	List of publications	153
	Donders Graduate School	154

GENERAL INTRODUCTION

Ben is a 60-year-old man who has been residing in a long-term care facility for a period of five years. His social network includes a younger sister and a former neighbor. When Ben was 10 years old, his parents divorced, and he subsequently lived with his mother. After graduating from high school, he attended art academy. Aged 22 years, he suffered his first psychosis and had to be hospitalized. Throughout his lifespan, Ben never engaged in professional employment. He dedicated his time to painting, receiving financial assistance from his mother. During his frequent depressive episodes, Ben began to abuse substances, including nicotine and alcohol. Ben experienced multiple episodes of psychosis throughout his life, necessitating regular hospitalizations. In the last 10 years, he began to exhibit a decline in personal care. His alcohol consumption increased, accompanied by a decline in nutritionally adequate food intake. In addition, he neglected his personal hygiene and responsibilities, including maintaining his home and caring for his pets. He also demonstrated a growing tendency to withdraw from social interaction. One day, the neighbor raised the alarm, reporting that Ben was lying in his house, confused and unable to walk. He was taken to the hospital and diagnosed with Wernicke's encephalopathy. After a brief period of hospitalization, he was transferred to a specialized diagnostic center.

KORSAKOFF'S SYNDROME

Korsakoff's syndrome (KS) is a devastating condition that in most patients occurs in the context of prolonged and severe alcohol use. The direct cause of KS is a deficiency of thiamine, but the syndrome can also occur in other conditions such as Hyperemesis Gravidarum in pregnant woman (Oudman et al., 2019), following bariatric surgery (Bento et al., 2023) or in other diseases that cause malnutrition (Oudman et al., 2024). Critical thiamine deficiency may result in Wernicke encephalopathy, an acute neurological disorder characterized by mental confusion, oculomotor abnormalities, and ataxia (Caine, 1997; Wijnia, 2022). KS is a neuropsychiatric disorder characterized by severe cognitive and behavioral impairments, resulting from incomplete recovery from Wernicke's encephalopathy, frequently due to delays in thiamine supplementation. Patients with KS show permanent diencephalic brain damage, especially in the anterior thalamic nuclei and the mamillary bodies (Arts et al., 2017). There is currently no universal consensus on the definition of KS, and debate centers on whether the description should be limited to severe amnesia in relation to other cognitive functions in an otherwise alert and responsive patient (Kopelman, 2022), or whether the definition should be expanded to include features such as executive dysfunction, problems with social cognition, apathy, lack of illness insight, and/or confabulation (Arts et al., 2017; El Haj, 2021). There is evidence suggesting that the cognitive profile of alcoholic KS may differ from that of non-alcoholic KS (Nikolakaros et al., 2018). This thesis focuses on the characteristics of alcoholic KS.

Living with Korsakoff's syndrome

The prevalence of KS is uncertain due to the fact that many individuals with severe alcohol use and cognitive impairment do not seek or receive care. A recent study in Finland showed an incidence of 3.7 per 100,000 men and 1.2 per 100,000 women (Palm et al., 2022). In the Dutch context, only limited and outdated data is available on the prevalence of KS, indicating a prevalence of 4.8 per 10,000 inhabitants (Blansjaar et al., 1987). In the Netherlands, there are specialized institutions for individuals with KS, which currently accommodate a total of approximately 1,350 individuals with KS (Korsakov Kenniscentrum, n.d.). These facilities are specialized long-term care facilities that provide 24-hour care for individuals diagnosed with KS. They offer a therapeutic residential environment, with objectives that include enhancing autonomy, safety, and quality of life. This includes provision of assistance to patients in activities that promote well-being, such as self-care and leisure, as well as support in the initiation and development of those activities. Two main

methodologies are central to an adequate KS therapeutic living environment: the empathic-directive approach and errorless learning.

The empathic directive approach is characterized by a positive and supportive attitude, in conjunction with a clear structure that encompasses routines and regularity, and a consistent pattern of behavior, offering clear directives and boundaries (Gerritsen et al., 2024). The errorless learning methodology relies on implicit learning mechanisms to enable patients to acquire new skills despite declarative memory impairments. This intervention has been studied in patients with KS, and its application contributes to autonomy and quality of life. (Rensen et al., 2017; Rensen et al., 2018). In specialized long-term care facilities, a multidisciplinary treatment team is often involved, including specially trained nurses, a geriatrician, psychologist, and occupational therapist. Somatic and psychiatric comorbidities are common in the long-term care population. Many patients lack the capacity to manage their own financial affairs, necessitating the involvement of a family member or professional administrator. In addition, almost all people with KS in long-term care have a formal or informal legal representative (Gerridzen & Goossensen, 2014).

CLINICAL CHARACTERISTICS

Neuropsychiatric symptoms and behavioral problems

Clinical descriptions of KS note that patients have limited insight into their own functioning: "the Korsakoff patients' common and often complete lack of true perception of their disease and handicapped functioning" as Blansjaar et al (1992) stated. And: "the patient believes that nothing is wrong with him" (Egger et al., 2002). A number of studies have shown that patients with KS rate their own limitations significantly lower than their clinicians (Walvoort et al., 2016; Bruijnen et al., 2021). Another study showed that among patients with KS in long-term care there was variation within the patient group, with about one-third of patients having no or mildly impaired awareness, one-third having moderately impaired awareness, and one-third having severely impaired awareness of their functional deficits (Gerridzen et al., 2019).

Another prevalent neuropsychiatric symptom of patients with KS is confabulation. Confabulations are memories of experiences and events that are misplaced in time and space, or never took place at all. Confabulations can be categorized into two distinct types: provoked confabulations and spontaneous confabulations.

Provoked confabulations refer to incorrect answers given to questions regarding an individual's past events, whereas spontaneous confabulations involve incorrect expressions that occur without an external trigger. As individuals who confabulate are unaware of the falsity of their statements, confabulations have been described as “honest lying.” Around 80% of the patients with KS are provoked confabulators, around 65% are spontaneous confabulators and around 60% of the patients with KS show both forms of confabulation. The presence of confabulations can manifests years after the onset of the syndrome. (Oudman et al., 2022; Rensen et al, 2023).

Apathy appears to be a common characteristic of individuals with KS yet it has only recently received attention in scientific literature. Individuals with apathy exhibit a pronounced decline in goal-directed activity relative to their previous level of functioning. This may be observed in various domains, including a reduction in social activity, diminished spontaneous emotions or emotional reactions, and a reduced level of general activity (Robert et al., 2018; Husain & Roiser, 2018; Ang et al., 2017). The consequences of apathy include diminished functional competence, elevated caregiver distress, accelerated cognitive decline, increased care needs, and even reduced life expectancy (Yeager & Hyer, 2008; Dufournet et al., 2019; Zuidema, et al., 2009; Nijsten et al., 2017).

It is also noteworthy that psychiatric comorbidity is a common occurrence in patients with KS. Nearly 60% of the KS patients have at least one comorbid psychiatric condition. Among these, mood disorders and psychotic disorders are the most prevalent (Gerridzen & Goossensen, 2014). In the aforementioned study population, nearly 71% of patients diagnosed with KS were prescribed one or more psychotropic drugs, in many cases with an unclear indication. The authors concluded that it seems probable that they are often given to manage neuropsychiatric symptoms, such as aggression or disinhibited behavior.

Cognitive profile

The primary feature of KS is amnesia, a severe *memory* impairment. Memory deficits are particularly evident in long-term declarative memory, primary in episodic memory processes. Both encoding and retrieval abilities are found to be impaired. Anterograde memory processes are more severely affected than retrograde memory processes and verbal memory is more severely affected than visuospatial memory. Patients with KS also show working memory deficits (Arts et al., 2017; Pitel et al., 2008; Kessels & Kopelman, 2012; Eikelboom et al., 2024; Oudman et al., 2019). Patients with KS are also impaired in orientation (Wester et al., 2013), but this

can slightly improve during the initial months following Wernicke encephalopathy (Bruijnen et al., 2021).

Deficits in executive functioning (EF) are frequently observed in patients with alcoholic KS. To illustrate, patients with KS display deficiencies in planning abilities, inhibition, problem-solving and cognitive flexibility (Brion et al., 2014; Oscar-Berman, 2012, Pitel et al., 2008). To date, only a limited number of studies have examined the prevalence of EF problems in KS. Two studies with small study populations have reported prevalence rates of 80% to 87% (van Oort & Kessels, 2008; Maharasingam et al., 2013) of the patients with KS scoring below threshold on at least one executive task. KS patients show similar levels of executive dysfunction as patients with non-amnesic alcohol-related cognitive impairment, suggesting that alcoholic neurotoxicity, not thiamine depletion may underly EF deficits (Janssen et al., 2023). Brion et al. (2014) provided an overview of studies on executive dysfunction in patients with KS and concluded that patients with KS appear to exhibit global impairment across different tasks that measure EF. However, the authors also noted that a comprehensive overview of the diverse EF impairments could not be established due to a lack of data and the fact that many studies used composite, unspecific EF tasks.

At the specialized diagnostic center, Ben agreed to undergo a neuropsychological assessment. This led to the following conclusion:
"The cognitive profile and severity of cognitive impairment are consistent with those observed in patients with Korsakoff's syndrome. Following a sufficient period of abstinence, there is a notable impairment in verbal long-term episodic memory, which encompasses both storage and retrieval of new information. Moreover, the patient showed mild deficits in sustained and divided attention, variable performance in executive functions, and mild impairments in social cognition. Additionally, the presence of limited illness insight, confabulations and apathy manifested as a lack of initiative, have been documented. In terms of differential diagnosis, a dementia syndrome is one possible explanation; however, the patient's history, with a clear decline in functioning since January, when Wernicke encephalopathy was presumed to have occurred, suggests a more probable classification of Korsakoff's syndrome. A follow-up examination is recommended when there are observations of further cognitive deterioration in the next few years."

Although there has been limited investigation of *social cognition* deficits in individuals with KS, the findings from existing studies suggest that patients with KS exhibit impairments in this domain. For instance, KS patients show diminished capacity to recognize facial expressions (Montagne et al., 2006). Patients with KS are found to be impaired in both cognitive and affective aspects of social cognition. More specifically, their capacity to recognize emotion, adopt the perspective of another individual, and understand socially challenging scenarios is significantly impaired (Drost et al., 2019).

The total IQ scores of patients with KS are lower than would be expected based on the estimated premorbid *intelligence*. With regard to the domains of the Wechsler Adult Intelligence Scale – IV (WAIS-IV), it is observed that the indices Perceptual Reasoning and Processing Speed are particularly affected. There is no evidence of decline on the Verbal Comprehension Index and the Working Memory Index (Haalboom et al., 2019).

EXECUTIVE FUNCTIONS

The present thesis focuses on the executive functioning of patients with KS. The term executive functions is a challenging cognitive construct to delineate, and it has been called an "umbrella term", which encompasses abilities such as planning, reasoning, problem-solving and goal-directed behavior (Lezak, 1982). It refers to higher order cognitive functions, responsible for controlling and managing other systems, abilities and processes. EFs are of great importance in almost every aspect of life, including mental and physical health, academic and vocational success, and quality of life (Diamond, 2013). EF is also closely related to the concept of fluid intelligence (i.e., reasoning; Van Aken et al., 2016).

Unity/diversity model of executive functions

One of the fundamental issues in comprehending the nature of EF is the debate surrounding its unity versus diversity. This debate concerns the manner in which the working mechanisms of EF are described: either as distinct components or as an entity functioning as a unitary system. Several authors have attempted to fractionate EFs into separate processes or components, including attention, emotion regulation, flexibility, inhibitory control, initiation, organization, planning, self-monitoring and working memory (Goldstein and Naglieri, 2013). EFs have thus been defined as a multifaceted construct that can be subdivided into multiple components. A considerable number of authors have proposed EF models with

varying numbers of factors, typically between two and five, identified using factor analysis (Anderson, 2002; Fisk and Sharp, 2004; Miyake et al., 2000; Hedden and Yoon, 2006; Adrover-Roig et al, 2007; Fournier-Vicente et al., 2008).

A recent and influential model describes EF in terms of both a unitary construct and shared but distinct functions. This unity/diversity model is proposed by Akira Miyake and Naomi Friedman, developed using factor analyses to detect latent variables underlying distinct executive tasks. In earlier studies, Friedman and Miyake identified three factors, including the factor inhibition (Miyake et al., 2000). They later redefined their model with a common EF factor (representing unity) that explained all the variation among the inhibition tasks, after which no inhibition-specific variance was found. An updating- and shifting-specific factor remained (Friedman and Miyake, 2017). The authors postulated that the common EF factor reflects the capacity to maintain and manage goals. Goal maintenance is a fundamental requirement of almost all EF tasks, with particular relevance to inhibition tasks. Effective goal maintenance necessitates the utilization of environmental cues to achieve these goals and the ability to neglect irrelevant stimuli. Furthermore, it is also necessary to retrieve and implement the appropriaKte goals at the appropriate time. The shifting-factor of EF is defined as the ability to substitute goals when necessary and to act expeditiously and effectively on the actual goals. Typically, this ability is assessed through tasks that require participants to quickly switch between subtasks in response to random cues. This process necessitates not only the selection of the appropriate task but also the capacity to replace it promptly within another task set. Friedman and Miyake (2017) hypothesized that the speed of this goal replacement is an individual difference which is the essence of the shifting-factor. The process of updating working memory involves the capacity to continuously replace information that is no longer relevant with information that is relevant when it is appropriate to do so, whilst preserving information that is still relevant. It also requires goal maintenance and cue-processing, to stop irrelevant information entering working memory.

Assessing executive function in clinical practice

A clinician seeking to examine EF in a patient suspected of having cognitive problems will typically administer a range of neuropsychological tasks to examine multiple cognitive domains, such as attention and memory. In regard to testing the domain of EF, fixed batteries such as the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) are frequently administered. These tasks evaluate multiple subcomponents of EF, with non-executive processes such as language and motor speed also affecting the outcomes of this tasks (Snyder et al., 2015).

The issue in question is also designated as the "task impurity problem" (Packwood et al., 2011). The ability to successfully complete an executive task necessitates the optimal functioning of the underlying basic processes, including attention, processing speed, and motor speed. Consequently, the final score on an executive task reflects performance on these cognitive primitives as well.

Another difficulty in assessing EF is the ecological validity and generalizability of commonly used executive tasks. A neuropsychological testing situation is by definition a controlled situation where the patient is often seated in a relatively quiet room, without distracting stimuli with tests containing specific instructions. This is at odds with the typical daily practice, which often involves ambiguity, multidimensional decision-making, unclear prioritization, and numerous distracting stimuli (Goldstein & Naglieri, 2013). Since neuropsychological assessment aims to predict actual performance in real-world contexts, ecological validity represents an essential criterion when assessing the quality of executive tasks. The concept of ecological validity encompasses both verisimilitude, which concerns the extent to which the conditions measured reflect those encountered in everyday life, and veridicality, which refers to the degree to which a measured skill accurately predicts performance in real-world situations (Bertens et al., 2023). Furthermore, numerous additional factors influence daily functioning, including motivation, physical impairments, and the use of compensatory strategies. It is therefore unsurprising that neuropsychological tests only offer a moderate prediction of real-world performance (Marcotte & Grant, 2010).

Executive dysfunction in patients with KS

In light of the aforementioned considerations regarding the concept of EF, it can be concluded that there are numerous open questions concerning executive dysfunction in patients with KS. For instance, the role of alcohol use in the development of EF remains unclear, and the profile of executive dysfunction in individuals with KS is still poorly understood. Brion et al. (2014) proposed incorporating the multifaceted nature of the concept of EF into new study designs and examining the separate executive components (shifting, updating, and inhibition) as process-pure as possible in individuals with KS. Furthermore, it can be debated whether executive dysfunction can be regarded as a central symptom of KS and thus should be included in the definition or classification criteria.

OBJECTIVES

The objective of this thesis is to examine the nature of executive dysfunction in individuals with KS. This includes the extent to which different aspects of EF are affected, the prevalence, and variability within the patient population. Furthermore, the dissertation examines the relationship between executive dysfunction and neuropsychiatric symptoms, with a particular emphasis on apathy. The study aims to contribute to the complex field of neuropsychological assessment in patients with KS.

THESIS OUTLINE

Following this introductory chapter, in **Chapter 2** is a systematic review of the literature is provided that focuses on the prevalence and severity of behavioral symptoms in people with KS. The study in **Chapter 3** investigates the degree of executive dysfunction in patients with KS for the three main executive subcomponents shifting, updating and inhibition/common EF, compared with healthy controls. Six computer-based tasks are included in the study. They are carefully designed to minimize the aforementioned "task impurity problem". Group differences and effect sizes are calculated in order to examine the relative severity of the impairment of each of the executive components.

The relation between executive dysfunction and neuropsychiatric symptoms is the focus of **Chapter 4**. First, the variance within the executive components will be explored by factor analysis to determine which factor structure of EF applies to KS patients. In order to consider the relative contribution of executive dysfunction beyond general cognitive impairment, the general cognitive functioning of individuals with KS is assessed with the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005).Second, the relationship between these cognitive measures and neuropsychiatric symptoms (measured by the Neuropsychiatric Inventory - Questionnaire, NPI, Kaufer et al., 2000; De Jonghe et al., 2003) will be examined using multiple hierarchical regression analysis.

The relationship between executive dysfunction and apathetic behavior, is the focus of **Chapter 5**. Here, executive dysfunction is measured at the behavioral level using an observational scale, the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A; Roth et al., 2005). Apathy and its subtypes (cognitive, behavioral, and emotoinal apathy) will be operationalized with the informant version of the Apathy Evaluation Scale (Marin et al., 1991).

Chapter 6 also examines the relationship between executive dysfunction, general cognitive functioning, and apathy. Here, EF is measured using tasks that are widely used in clinical practice. Apathy and its subtypes are measured using the informant version of the Apathy Motivation Index (Ang et al, 2017). The relationship between the constructs will be calculated using regression analysis and comparing, at the group level, apathetic and non-apathetic individuals with KS in terms of their scores on the executive tasks.

In **Chapter 7**, the main findings will be summarized and discussed. This chapter will also include a discussion of the strengths and limitations of the study, as well as recommendations for future research. Additionally, clinical recommandations will be made.

Ben moved to a long-term care expertise center for patients with Korsakoff's syndrome. In this facility, he engages in the same daily schedule on a consistent basis. The consistency of this routine is of significant benefit to Ben. In the event of unanticipated incidents, it is observed that Ben reacts with agitation; thus, such occurrences are avoided as much as possible. Ben himself has frequently stated that he does not know why he has been hospitalized and that he will soon go back to his previous living situation. He also frequently states that he misses painting, yet when presented with the opportunity to do so, he declines. Fortunately, Ben has never experienced another psychotic episode and adheres strictly to his medication regimen. Ben continues to interact with others minimally, yet he has recently reacquired a pet cat in his apartment. The care staff provides him with daily reminders to care for the cat and assists to keep his apartment clean. When asked about his life, Ben states, "It is nice that I still have my cat."

1

Chapter 2

Prevalence and severity of behavioural symptoms in patients with Korsakoff syndrome and other alcohol-related cognitive disorders: a systematic review

Gerridzen, I. J., Moerman-van den Brink, W. G., Depla, M. F., Verschuur, E. M. L., Veenhuizen, R. B., Wouden, J. C., Hertogh, C. M. P. M., & Joling, K. J. (2017). Prevalence and severity of behavioural symptoms in patients with Korsakoff syndrome and other alcohol-related cognitive disorders: A systematic review. *International Journal of Geriatric Psychiatry, 32*(3), 256–273. https://doi.org/10.1002/gps.4636

SUMMARY

Objective

Experiences from clinical practice suggest that behavioural symptoms in patients with Korsakoff syndrome (KS) are a frequent problem. Knowledge about behavioural symptoms is important in understanding and managing these symptoms. The aim of this study is to review the prevalence and severity of behavioural symptoms in KS.

Methods

Relevant articles were identified by searching Medline (PubMed), PsycINFO, Embase and CINAHL up to 4 June 2014. Two reviewers independently selected the studies, extracted their baseline data and assessed methodological quality using a standardized checklist.

Results

Fifteen studies fulfilled the inclusion criteria. A diversity of diagnoses was used indicating that KS and other alcohol-related cognitive disorders and terms were used interchangeably. None of the studies were primarily designed to estimate the prevalence or severity of behavioural symptoms in patients with KS. Most studies had serious methodological limitations. The reported prevalence estimates of behavioural symptoms in the included studies varied strongly. Most prevalent were depressive symptoms and disorders (2–50%, median 27%) and agitation and aggression (10–54%, median 27%). None of the reported, mean severity estimates met pathological thresholds. The highest severity estimates were found for apathy.

Conclusions

Good quality studies on behavioural symptoms in patients with KS are lacking. Observational research designed to provide reliable estimates of the prevalence and severity of behavioural symptoms in patients with KS is needed. This could improve understanding and managing these symptoms and help care staff to better support the needs of this specific patient group.

INTRODUCTION

Wernicke–Korsakoff syndrome (WKS) is a symptom complex in which acute Wernicke encephalopathy (WE) proceeds, if untreated, to death in up to 20% of cases, or to the chronic Korsakoff syndrome (KS) in 85% of survivors (Thomson et al., 2012; Thomson and Marshall, 2006; Victor et al., 1989). WKS usually occurs in alcoholics and is caused by malnutrition and the associated thiamine deficiency. Only 20% recover completely and up to 25% do not show any improvement in cognitive functioning and will require long-term institutionalization (Kopelman et al., 2009; Victor et al., 1989). Studies on the prevalence and incidence of KS are very limited. Ramayya and Jauhar (1997) reported a KS incidence in Glasgow, Scotland, of around 5 per 100 000 between 1990 and 1995. In The Hague, The Netherlands, a KS point-prevalence of 48 per 100 000 inhabitants has been found (Blansjaar et al., 1987). It is estimated that about 1200 patients with KS are residing in Dutch specialist long-term care facilities (LTCFs) (www.korsakovcentrum.nl).

Clear diagnostic criteria for KS are lacking, and KS is often used interchangeably with alcohol-related dementia (ARD) and other alcohol-related cognitive disorders. In the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM), KS is classified as 'alcohol-induced persisting amnestic disorder' (American Psychiatric Association, 2000). The DSM-5 (2013) categorized KS as 'alcohol-induced major or mild neurocognitive disorder'. Oslin et al. (1998) proposed clinical criteria for ARD, which may include cases of WKS and also other cases of dementia that appear to be alcohol-related. To reflect the heterogeneity of alcohol-related cognitive disorders, the umbrella terms 'alcohol-related brain damage' (ARBD) or 'alcohol-related brain injury' are increasingly used (Jauhar and Smith, 2009; Ridley et al., 2013). The varying terminology and conceptualizations of KS, ARD and other alcohol-related cognitive disorders hampers the possibility to identify clearly defined population studies for scientific purposes.

Korsakoff syndrome is characterized by severe deficits in long-term explicit memory, both in anterograde and retrograde memory and is often associated with confabulation. The episodic aspect of memory is specifically affected (Kessels and Kopelman, 2012). Executive functioning is also commonly impaired (Brion et al., 2014; Maharasingam et al., 2013; Van Oort and Kessel, 2009). Overall intelligence, attention and implicit or procedural memory as well as short-term memory usually remain intact (Kessels and Kopelman, 2012; Kopelman, 1995; Kopelman et al., 2009; Oscar-Berman, 2012). A lack of insight into their own disease has also been noticed in

clinical practice as a characteristic of KS patients, although this has not been subject to much research (Egger et al., 2002; Thomson et al., 2012; Victor et al., 1989).

In addition to the cognitive deficits, behavioural symptoms, such as aggression and apathy or lack of initiative, have been noticed from the earliest reports of the disease and have also been mentioned in some more recent studies amongst KS patients (Blansjaar et al., 1987; Egger et al., 2002; Gerridzen and Goossensen, 2014; Ridley et al., 2013; Thomson et al., 2012; Victor et al., 1989). Sergei S. Korsakoff, a Russian physician who was the first to describe KS, observed that in some KS cases, the predominant features were increased irritability and agitation (Victor and Yakovlev, 1955). In other cases, confusion predominated, either apathetic or associated with excitement (Talland, 1960; Victor et al., 1989). Egger et al. (2002) described patients with KS as follows: 'They are often very indifferent and are lacking initiative in performing the simplest daily activities. Furthermore, they are very slow, a-practical and apathetic. Lack of insight into oneself and one's disease often completes the picture'.

Cognitive functioning, in particular memory, and to a lesser extent executive functioning have been studied extensively in patients with KS, yet studies addressing behavioural symptoms in KS patients are scarce. Although evidence is lacking, staff caring for KS patients frequently encounter behavioural symptoms and experience these symptoms as very challenging (Blansjaar et al., 1992; Gerridzen and Goossensen, 2014; Victor et al., 1989). A better insight into behavioural disturbances in KS patients may help care staff to understand and manage challenging behavioural symptoms. Therefore, the aim of this systematic review was to describe the prevalence and severity of behavioural symptoms, thereby focusing primarily on KS. However, given the controversy on diagnosis, other alcohol-related cognitive disorders were also taken into consideration, and the term KS was used as an umbrella term.

METHODS

Data sources and search strategy

This review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher et al., 2009). A comprehensive literature search was conducted in the databases Medline (PubMed), PsycINFO, Embase and CINAHL. MeSH terms (PubMed), Thesaurus terms (PsychINFO, Embase, CINAHL) and free text words were used for the search. The search strings combined two separate domains: (1) 'Korsakoff syndrome' or

'alcohol amnestic syndrome' or 'Wernicke encephalopathy'; and (2) a wide range of behavioural symptoms. The search period was from inception of the databases up to 4 June 2014. The PubMed search strategy is presented in Appendix I. Comparable search strategies were undertaken in the other databases and are available from the authors. The results of the searches were entered into a Reference Manager database. Duplicates were removed, and the unique references were included for further selection procedure.

Selection criteria

Articles were included if they met all of the following criteria:

1) The study included patients with a diagnosis of KS. Given the aforementioned diagnostic difficulties, patients with other alcohol-related cognitive disorders such as ARD and ARBD were also included.
2) The study reported primary research data on behavioural symptoms.
3) The study included at least 10 patients.
4) The study was written in the English, Dutch or German language.
5) The study was on humans.

Selection procedure

Titles and abstracts of the references retrieved from the searches were screened by two reviewers independently (I.G. and W.M.) according to the selection criteria. If the reviewers were uncertain about data from the title and abstract, the full text was obtained. After screening the full texts, both reviewers made the definitive selection independently based on the aforementioned selection criteria. Discrepancies between the two selections were discussed until consensus was reached. In case of persistent disagreement, a third reviewer (K. J.) was consulted. In addition to the search strategy, the reference lists of the selected articles were reviewed to identify any relevant publications that had not been found in the searches.

Data extraction and analysis

Full text articles of all selected studies were obtained for further examination. Both reviewers (I.G. and W.M.) extracted data from the included articles independently using a predefined data extraction form. The extracted data included diagnosis and the diagnostic criteria that were used, study design, study setting, study population, inclusion and/or exclusion criteria, method of data collection, behavioural measurement instrument and outcomes. Authors were contacted when insufficient data were provided. Given the heterogeneity of the included studies, we decided not to pool data, but to only provide medians and ranges of the estimates.

Assessment of methodological quality

For this study, both reviewers (I. G. and W.M.) assessed the methodological quality of the included studies using Boyle's guidelines for evaluating prevalence studies (Boyle, 1998). This checklist comprises eight criteria (Appendix II). Each paper was rated according to these criteria, with one point being given if the criteria were fulfilled. Zero points were allocated if the criteria were not fulfilled, not reported or unclear. Disagreement between reviewers was resolved by discussion or the third reviewer was consulted if required.

RESULTS

Study selection

The search strategy yielded 4163 articles. After removing duplicates, a list of 2967 articles remained of which 2873 were excluded based on title and abstract. After reading the full text of the remaining 94 articles, 13 studies fulfilled the selection criteria (Alderdice et al., 1994; Blansjaar et al., 1992; Cheon et al., 2008; Draper et al., 2011; Egger et al., 2002; Ganzevles et al., 1994; Gerridzen and Goossensen, 2014; Lennane, 1986; Oudman and Zwart, 2012; Plutchik and DiScipio, 1974; Schepers et al., 2000; Wijnia et al., 2012; Wilson et al., 2012). Two articles, identified through reviewing the reference lists of the selected articles, also met the selection criteria (Ferran et al., 1996; Price et al., 1988). The study of Ferran et al. (1996) was not identified by the electronic search. The study of Price et al. (1988) was not identified because the journal it was published in is not included in the electronic databases. As a result, 15 articles were included for analysis in this review. Figure 1 presents the flow chart of the selection process and reasons for exclusion.

Characteristics of the included studies

Table 1 provides an overview of the characteristics of the 15 included studies. Ten of the studies had a cross-sectional design, and five studies used a longitudinal study design. Only Cheon et al. (2008) and Wilson et al. (2012) reported longitudinal data on behavioural symptoms. Samples sizes ranged from 10 (Alderdice et al., 1994) to 556 patients (Gerridzen and Goossensen, 2014), with a median of 44. Except for one study (Cheon et al., 2008), all studies were conducted in the Netherlands, the UK, the USA and Australia. The studies included were conducted in various settings varying from psychiatric hospitals and nursing homes to dedicated ARBD services. Seven of them involved specialist Korsakoff wards of which five are in nursing homes (Blansjaar et al., 1992; Gerridzen and Goossensen, 2014; Oudman and Zwart, 2012; Schepers et

al., 2000; Wijnia et al., 2012) and two are in psychiatric hospitals (Egger et al., 2002; Ganzevles et al., 1994), all located in the Netherlands.

Participant exclusion criteria varied, with two studies excluding participants with other DSM-IV Axis I disorders (Cheon et al., 2008) and active psychotic symptoms (Plutchik and DiScipio, 1974). Three studies excluded participants aged 65 years and over (Blansjaar et al., 1992; Ferran et al., 1996; Wilson et al., 2012). The study of Draper et al. (2011) excluded participants younger than 50 years. The alcohol-abstinence period before subjects were assessed varied from ≥7 to ≥60 days or was not reported.

A diversity of diagnoses was used in the included studies, varying from KS, alcohol amnestic disorder, amnestic syndrome due to alcohol, KS, Wernicke– Korsakoff disease and WE (Alderdice et al., 1994; Blansjaar et al., 1992; Draper et al., 2011; Egger et al., 2002; Gerridzen and Goossensen, 2014; Lennane, 1986; Plutchik and DiScipio, 1974; Schepers et al., 2000; Wijnia et al., 2012). The diagnoses ARD, ARBD and alcoholic dementia (Alderdice et al., 1994; Cheon et al., 2008; Draper et al., 2011; Ferran et al., 1996; Lennane, 1986; Price et al., 1988; Schepers et al., 2000; Wilson et al., 2012) were also used with overlapping diagnoses. Lennane (1986) used the terms ARBD, alcohol-related amnestic syndrome, KS and WKS interchangeably. These diagnoses were classified using different classification systems such as DSM-III-R (Blansjaar et al., 1992; Ganzevles et al., 1994), DSM-IV (Egger et al., 2002; Schepers et al., 2000), DSM-IV-TR (Wijnia et al., 2012), ICD-10 (Ferran et al., 1996) and ICD-10-AM (Draper et al., 2011). In two studies (Cheon et al., 2008; Wilson et al., 2012), diagnosis was based on criteria according to Oslin et al. (1998). In the study of Oudman and Zwart (2012), diagnosis was based on DSM-IV-TR and criteria according to Kopelman et al. (2009). In five studies, it was unclear how the diagnosis had been established (Alderdice et al., 1994; Gerridzen and Goossensen, 2014; Lennane, 1986; Plutchik and DiScipio, 1974; Price et al., 1988).

In addition to this, patients were at different stages of their disease varying from the onset (Ferran et al., 1996) to the chronic phase (Blansjaar et al., 1992; Gerridzen and Goossensen, 2014; Oudman and Zwart, 2012; Plutchik and DiScipio, 1974; Schepers et al., 2000; Wijnia et al., 2012).

Methodological quality

As shown in Table 2, according to the Boyle criteria (Boyle, 1998), most of the included studies received low ratings for methodological quality. Although the target population was clearly defined in 67% of the studies, most studies did not fulfil or report on the other criteria.

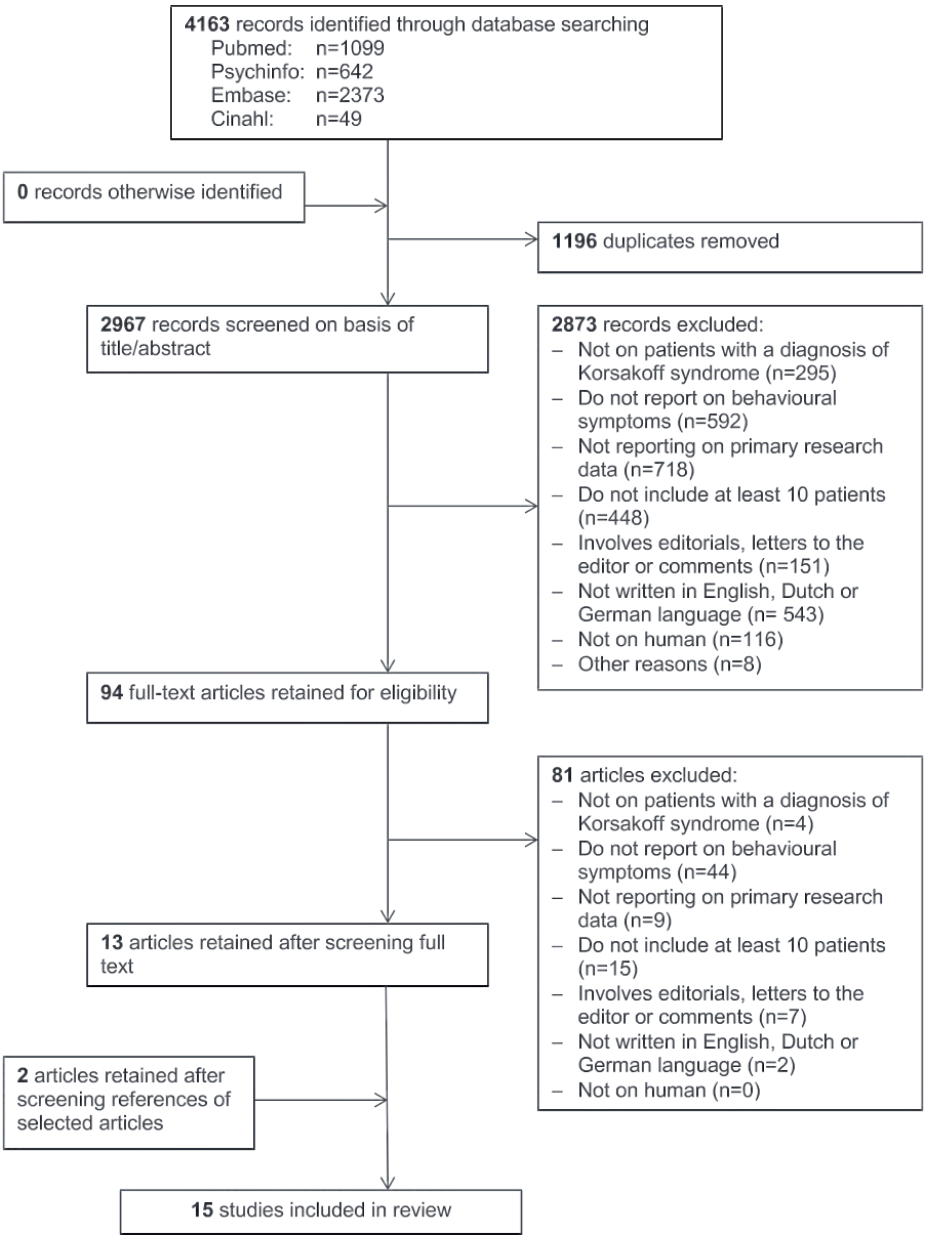

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart of the literature search and selection phase including reasons for exclusion.

The prevalence of behavioural symptoms

A total of 10 studies reported on the prevalence of behavioural symptoms. Table 3 presents the prevalence estimates reported in the included studies. We distinguished the following categories: psychotic symptoms and disorders, affective symptoms and disorders, agitation and aggression and other symptoms. Two studies reporting on prevalence used an assessment instrument (Price et al., 1988; Wilson et al., 2012). In the other studies, prevalence estimates were nearly all obtained clinically. The time period during which these estimates were measured was often unknown. One study did not report how prevalence was assessed (Lennane, 1986).

Psychotic symptoms and disorders

As shown in Table 3, nine studies described 15 prevalence estimates on psychotic symptoms and disorders, ranging from 0% (Ferran et al., 1996) to 87% (Wilson et al., 2012) with a median of 10%. Some studies reported on psychiatric disorders such as schizophrenia while others reported on psychotic symptoms such as hallucinations and delusions. The study of Wilson et al. (2012) constituted an outlier with a very high prevalence estimate of 87% of confabulations, hallucinations or delusions in patients with ARBD as measured with the Health of the Nation Outcome Scale-Acquired Brain Injury (HoNOS-ABI) within the first year of referral to the ARBD service.

Affective symptoms and disorders

Nine studies reported 12 prevalence estimates on depressive symptoms and disorders ranging from 2% (Blansjaar et al., 1992; Wilson et al., 2012) to 50% (Alderdice et al., 1994) with a median of 27%. Four studies reported on anxiety and anxiety disorders with five prevalence estimates ranging from 5% (Blansjaar et al., 1992; Schepers et al., 2000) to 27% (Ferran et al., 1996) with a median of 6%. One study reported about anxiety and paranoia with a prevalence estimate of 5% (Blansjaar et al., 1992).

Agitation and aggression

Only three studies reported on agitation and aggression with five prevalence estimates ranging from 10% (Schepers et al., 2000) to 54% (Ferran et al., 1996) with a median of 27%. In one study, a prevalence estimate of 13% was found for aggression and suspiciousness (Schepers et al., 2000).

Table 1. Study characteristics of the included studies (N=15)

Author/Year/ Country (Reference Nr)	**Design**	**Aim of the study**	**Study sample and setting**
Alderdice et al. (1994), UK (#1)	Cross-sectional, observational	To identify specific subtypes of drinkers on the basis of their neuropsychological performance using cluster analysis.	N=88 Organic brain damage related to alcohol abuse (hospital) n=10: • KS n=4 • Alcoholic dementia n=1 • Non-specific diagnosis of chronic alcoholism n=5 Social drinkers n=20 Problem drinkers n=58
Blansjaar et al. (1992), the Netherlands (#2)	Longitudinal, observational	To define the course of both cognitive and social impairment of patients with alcohol amnestic disorder under different conditions over three years.	N=44 Alcohol amnestic disorder: • Alcohol clinic n=14 • Specialist Korsakoff ward nursing home n=16 • Sheltered Korsakoff accommodation n=14
Cheon et al. (2008), Korea (#3)	Longitudinal, trial	To measure the cognitive functions of patients with alcoholic dementia before and after 12 week treatment with memantine.	N=19 Probable alcohol-related dementia (hospital, department of psychiatry)
Draper et al. (2011), Australia (#4)	Cross-sectional, observational	To document the prevalence of alcohol-related dementia, Wernicke's encephalopathy and amnestic syndrome due to alcohol and to describe the principal reasons for admission, medical comorbidities, interventions and outcomes of patients admitted with alcohol-related cognitive impairment.	N=462 (public hospitals) Alcohol-related dementia n= 300 Wernicke's encephalopathy n=77 Amnestic syndrome due to alcohol n=126 (With overlapping diagnoses)
Egger et al. (2002), the Netherlands (#5)	Cross-sectional, observational	To compare MMPI-2 profiles of Korsakoff patients with an alcohol-dependent non-Korsakoff group.	N=40 (psychiatric hospital) KS n=20 (specialist Korsakoff ward) Alcohol-dependent non-Korsakoff n=20 (addiction ward)
Ferran et al. (1996), UK (#6)	Cross-sectional, observational	To describe clinical characteristics and service use of patients with early onset dementia.	N=200 Early-onset dementia service: (in- and outpatients) • Alcohol-related dementia n=12 • 'Other diagnosis' n=36 (including 3 patients with KS) • Alzheimer's n=54 • Depression n=36 • Vascular n=33 • Unspecified n=17 • Frontal lobe dementia n=7 • Cortical Lewy Body Disease n=4 • Not known n=1

Criteria diagnosis 'KS'	Patient characteristics	Abstinence period	Inclusion criteria
Not given	Organic brain damage: Gender (M/F) 9/1 Mean age 63, SD±12	Not given	
DSM-III-R	Alcohol amnestic disorder: Gender (M/F) 29/15 Mean age 52, SD±8,1	≥ 1 month	≤ 65 years
Oslin	Alcohol-related dementia: Gender (M/F) 18/1 Mean age 57.37, SD± 7.90 Range 35-66	≥ 60 days	No other DSM-IV Axis I disorder
ICD-10-AM	Alcohol-related dementia: Gender (M/F) 246/54 Mean age 65, SD±9.3 Range 50.4-86.6	Not given	≥ 50 years
DSM-IV	KS: Gender (M/F) 18/2 Mean age 49.9, SD±9.7	Not given	
ICD-10	Early-onset dementia: Gender (M/F) 116/84 Mean age 56, SD±9.28 Range 25-71 Alcohol related dementia: not given KS: not given	Not given	Dementia-onset ≤ 65 years

Table 1. Continued

Author/Year/ Country (Reference Nr)	**Design**	**Aim of the study**	**Study sample and setting**
Ganzevles et al. (1994), the Netherlands (#7)	Cross-sectional, observational	To compare the effect of specialist Korsakoff wards on cognitive and behavioral aspects of patients with KS in a general psychiatric hospital.	N=36 Alcohol amnestic disorder (n=24) • Specialist Korsakoff ward psychiatric hospital (K-group) n=12 • General ward psychiatric hospital (P-group) n=12 • Healthy subjects n=12
Gerridzen and Goossensen (2014), the Netherlands (#8)	Cross-sectional, observational	To describe baseline characteristic, comorbidity, and the use of psychotropic drugs of patients with KS living in LTCFs.	N=556 KS and other alcohol-related cognitive impairment (specialist Korsakoff wards nursing homes)
Oudman and Zwart (2012), the Netherlands (#10)	Cross-sectional, observational	To compare different aspects of Quality of Life in patients with KS and compare this with patients with dementia from the same care facilities.	N=147 KS (specialist Korsakoff ward nursing home) n=72 Dementia (nursing home) n=75
Plutchik and DiScipio (1974), USA (#11)	Cross-sectional, observational	To compare personality profiles between patients with chronic alcoholism (KS), patients with chronic schizophrenia, and geriatric patients with chronic brain syndrome.	N=60 Chronic alcoholism with KS (long-term psychiatric patients in hospital) n=10 Schizophrenia (long-term psychiatric ward) n=30 Chronic brain syndrome (geriatric ward mental hospital) n=20
Price et al. (1988), Australia (#12)	Longitudinal, observational	To assess the characteristics of patients with alcohol-related brain damage who do badly after discharge into the community.	N=37 Alcohol-related brain damage (including 21 patients with KS) (psychiatric or rehabilitation units and non-psychiatric facilities)
Schepers et al. (2000), the Netherlands (#13)	Cross-sectional, observational	To describe characteristics, comorbidity and mortality of patients with KS after admission to a nursing home.	N=77 KS or alcohol amnestic disorder (including 4 patients with alcohol dementia) (specialist Korsakoff ward nursing home)
Wijnia et al. (2012), the Netherlands (#14)	Cross-sectional, observational	To examine the symptoms that preceded the KS.	N=128 KS (specialist Korsakoff ward nursing home)
Wilson et al. (2012), UK (#15)	Longitudinal, observational	To describe the clinical presentation, course and psychosocial outcome of patients with alcohol-related brain damage referred to a tertiary service.	N=41 Alcohol-related brain damage (tertiary service for alcohol-related brain damage, in- and outpatients)

Criteria diagnosis 'KS'	Patient characteristics	Abstinence period	Inclusion criteria
DSM-III-R	KS: Gender (M/F) not given Mean age K 51.1, SD±6.1 Mean age P 56.1, SD±4.9	Not given	
Not given	KS: Gender (M/F) 415/141 Mean age 62.8, SD±8.4 Range 40.8-85.8	Not given	
DSM-IV-TR Kopelman	KS: Gender (M/F) 62/10 Mean age 61.1, SD±8.2	Not given	
Not given	KS: Gender (M/F) 8/2 Mean age 56.3 Range 40-66	Not given	No active psychotic delusions or hallucinations
Not given	Alcohol-related brain damage: Gender (M/F) 29/8 Mean age 55.1 Range 40-65	Until the sensorium was entirely clear (≥ 5 days and ≤ 5 months)	
DSM-IV	KS: Gender (M/F) 55/22 Mean age 53, SD±8.9 Range 34-73	Not given	
DSM-IV-TR	KS: Gender (M/F) 105/23 Mean age 58.7 Range 33-87	Not given	
Oslin	Alcohol-related brain injury: Gender (M/F) 30/11 Mean age 54 Range 43-68 Mean age male 59.9 Mean age female 50.1	Not given	≤ 65 years

Table 2. Methodological quality of the included studies (N=15) (Boyle, 1998)

Reference (#)	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	Total (%)
1. Was the target population defined clearly?	0	0	1	1	1	0	1	1	1	1	0	0	1	1	1	66.7
2. Was probability sampling used to identify potential respondents?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3. Did characteristics of respondents match the target population?	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	6.7
4. Were the data collection methods of behavioural symptoms standardized?	0	1	1	0	0	0	0	0	0	1	0	0	1	0	0	26.7
5. Was the measure of behavioural symptoms reliable?	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	13.3
6. Was the measure of behavioural symptoms valid?	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	6.7
7. Were special features of sampling design accounted for in the analysis?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8. Did the reports include confidence intervals for statistical estimates?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 = not fulfilled, not reported or unclear; 1 = fulfilled.

Other symptoms

Apathy was reported in one study with a prevalence estimate of 8% (Schepers et al., 2000). Disinhibition, insomnia, recklessness and wandering were reported only by Ferran (Ferran et al., 1996) with prevalence estimates of 36%, 18%, 18%, and 27%, respectively.

The severity of behavioural symptoms

A total of six studies reported on the severity of behavioural symptoms. Table 4 presents the severity estimates reported in the included studies. Different assessment instruments were used to measure severity. Of these, only the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) and the Behaviour Observation Scale for patients with KS (GOK) (Ganzevles et al., 1994) were primarily developed to assess behavioural symptoms. The GOK is a Dutch, non-validated instrument, which has been used once (Ganzevles et al., 1994).

Psychotic symptoms

In the study of Blansjaar et al. (1992), none of the mean scores of the Brief Psychiatric Rating Scale-Expanded (BPRS-E) items on psychotic symptoms were above the pathological thresholds (score of ≥4) (Table 4). The items 'grandiosity' and 'disorientation' scored highest. Lack of insight into the disease was also covered in the item 'grandiosity'. Blansjaar et al. (1992) reported that on the item 'grandiosity', pathological scores were reached in 47% of all ratings. In the study of Cheon et al. (2008), the NPI domains 'delusions' and 'hallucinations' scored also low. In this study, the cut-point indicating the presence of clinically relevant symptoms (usually ≥4) was not clear. Also, Egger et al. (2002) found no pathological mean scores on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2). In the study of Plutchik and DiScipio (1974), the mean percentile score on the Emotions Profile Index (EPI) item 'distrustful' was also low.

Table 3. Prevalence estimates of behavioural symptoms amongst Korsakoff patients reported by the included studies (N=10)

Behavioural symptom		**Study reference (# Nr)**
Psychotic symptoms and disorders	Delusions	*#6*
	Hallucinations	*#1*
	Cluster alcoholic dementia	
	Cluster mild alcoholic Korsakoff	*#1*
		#6
	Confabulations, hallucinations or delusions	*#15*
		#15
	Psychosis / hallucinations	*#14*
	Paranoid psychosis	*#9*
		#15
	Mania	*#6*
	Psychotic disorder	*#4*
		#8
	Chronic	*#13*
	Acute	*#13*
	Schizophrenia	*#2*
Affective symptoms and disorders	Depression	*#1*
	Cluster alcoholic dementia	
	Cluster mild alcoholic Korsakoff	*#1*
		#6
		#12
		#14
		#15
	Depression or other mental health problems	*#15*
	Major depression	*#2*
	Depressive illness	*#9*
	Depressive disorder Acute	*#13*
	Bipolar affective disorder	*#15*
	Mood disorder	*#8*
	Anxiety disorder	*#2*
		#8
	Anxiety	*#6*
	Chronic	*#13*
	Acute	*#13*
	Anxiety and paranoia	*#2*

Reported prevalence		Behavioural measure	
%	Period of time measured	Assessment instrument	Other*
27	From onset of disease until latest contact with service		2,5
25	Unknown		1
25	Unknown		1
0	From onset of disease until latest contact with service		2,5
87	Within the first year of referral to service	HoNOS-ABI[c]	
35	After an average of 24 month after referral to service	HoNOS-ABI[c]	
7	Unknown		1
9	Unknown		Not given
5	Unknown		1,4
27	From onset of disease until latest contact with service		2,5
10	Including residual and late onset		Database for hospital episodes[a]
18	Unknown		1,2
4	Diagnosed during admission		2, CvZ-V[b]
8	Diagnosed during admission		2, CvZ-V[b]
2	At the start of the study		1,2,3,4
25	Unknown		1
50	Unknown		1
36	From onset until latest contact with service Around discharge from inpatient care		2,5
46	Unknown	HAM-D[d]	
18	Unknown		1
42	On referral to the service		1,4
29	After an average of 24 months after referral to service	HoNOS-ABI[c]	
2	At the start of the study		1,2,3,4
7	Unknown		Not given
12	Diagnosed during admission		2, CvZ-V[b]
2	On referral to the service		1,4
32	Unknown		1,2
5	At the start of the study		1,2,3,4
6	Unknown		1,2
27	From onset of disease until latest contact with service		2,5
5	Diagnosed during admission		2, CvZ-V[b]
14	Diagnosed during admission		2, CvZ-V[b]
5	At the start of the study		1,2,3,4

Table 3. Continued

Behavioural symptom		Study reference (# Nr)
Agitation and aggression	Agitation	*#6*
	Chronic	*#13*
	Acute	*#13*
	Aggression	*#6*
		#15
	Aggression and suspiciousness Acute	*#13*
Other symptoms	Apathy Acute	*#13*
	Disinhibition	*#6*
	Insomnia	*#6*
	Recklessness	*#6*
	Wandering	*#6*

* 1 = Medical history; 2 = Medical record; 3 = Biography; 4 = Clinical examination; 5 = Reports of patients, carers and clinicians.

[a] The New South Wales Admitted Patient Care Database for hospital episodes in public and private hospitals. In this study diagnoses are based on the International Classification of Diseases (ICD-10-AM).

[b] The Dutch standard of classification of diseases for nursing homes (CvZ-V) is based on the International Classification of Diseases (ICD-10).

[c] HoNOS-ABI = Health of the Nation Outcome Scale-Acquired Brain Injury: 4 subscales, 12 items, ranging from 0 "no problem" to 4 "severe to very severe problem", total score 0-48, ratings (of items) of 0 and 1 require no action (not clinically significant), ratings of 2, 3, and 4 do (clinically significant).

[d] HAM-D = Hamilton's Depression Rating Scale: 21 items, only the first 17 are scored either on a 5-point (0-4) or a 3-point (0-2) scale, total score (0-52) ≥ 8 indicate depression.

Affective symptoms

Affective symptom scores above pathological thresholds on the individual items of the BPRS-E were mainly observed on the items 'anxiety' and 'depression' (Blansjaar et al., 1992). However, none of the mean scores of the BPRS-E items on affective symptoms were pathological. In the other studies, mean scores were also low or not pathological.

Agitation and aggression

In the study of Blansjaar et al. (1992), the mean scores on the BPRS-E items 'hostility', 'uncooperativeness' and 'tension' again scored not pathological. The authors noted that the rating on 'uncooperativeness' was remarkably higher on patients residing in nursing homes. The NPI domain 'agitation/aggression' scored low in the study of Cheon et al. (2008). The mean percentile on the item 'aggressive' scored also low on the EPI (Plutchik and DiScipio, 1974).

Reported prevalence		Behavioural measure	
%	**Period of time measured**	**Assessment instrument**	**Other***
27	From onset of disease until latest contact with service		2,5
10	Diagnosed during admission		2, CvZ-V[b]
40	Diagnosed during admission		2, CvZ-V[b]
54	From onset of disease until latest contact with service		2,5
20	On referral to the service		1.4
13	Diagnosed during admission		2, CvZ-V[b]
8	Diagnosed during admission		2, CvZ-V[b]
36	From onset of disease until latest contact with service		2,5
18	From onset of disease until latest contact with service		2,5
18	From onset of disease until latest contact with service		2,5
27	From onset of disease until latest contact with service		2,5

Other symptoms

Severity estimates on apathy varied widely. In the study of Blansjaar et al. (1992), the item 'blunted affect' on the BPRS-E scored low in contrast to the relatively high scores on the NPI item 'apathy' (Cheon et al., 2008) and QUALIDEM item 'having something to do' (Oudman and Zwart, 2012). In the study of Plutchik and DiScipio (1974), the mean percentile on 'timid' on the EPI scored high. Items concerning other behavioural symptoms often scored low on severity.

Table 4. Severity estimates of behavioural symptoms amongst Korsakoff patients reported by the included studies (N=6)

Reported Severity (score ± SD)					
BPRS-E (mean scores) (Blansjaar et al., 1992)		**MMPI-2 (mean T-scores or percentile scores) (Egger et al., 2002)**		**NPI[a] (mean scores) (Cheon et al., 2008)**	
Total score	34.5±0.6	*Clinical scales:*		T0*:	
Somatic concern	1.6±0.9	Hypochondriasis	51.2±13.3	Total score	12.3±5.2
Anxiety	1.4±0.7	Depression	54.0±8.9	Mean score	1.0±1.1
Depression	1.8±1.1	Hysteria	53.0±13.7	Delusions	0.6±1.2
Guilt	1.4±0.5	Psychopathic deviate	60.0±14.5	Hallucinations	0.2±0.9
Hostility	1.2±0.4	Masculinity/ femininity	53.7±11.1	Agitation/ aggression	0.7±1.6
Suspiciousness	1.2±0.4	Paranoia	53.8±12.4	Depression/ dysphoria	2.6±2.0
Unusual thought content	1.2±0.6	Psychasthenia	53.2±10.3	Anxiety	1.1±1.4
Grandiosity	3.1±1.1	Schizophrenia	54.9±11.2	Elation/ euphoria	0.0±0.0
Hallucinations	1.1±0.2	Hypomania	55.0±8.6	Apathy/ indifference	3.4±3.2
Disorientation	3.5±1.3	Social introversion	48.7±11.5	Disinhibition	0.8±1.4
Conceptual disorganization	1.2±0.5			Irritability/ lability	1.0±1.5
Excitement	1.5±0.6	*Content scales:*		Aberrant motor behaviour	0.0±0.0
Motor retardation	1.0±0.1	Anxiety	55.2±10.4	Sleep/night-time behaviour	1.7±2.0
Blunted affect	1.0±0.1	Fears	49.6±11.5	Appetite/eating disorders	0.0±0.0
Tension	1.1±0.4	Obsessiveness	55.6±11.3		
Mannerisms and posturing	1.2±0.4	Depression	57.9±10.0	T1**:	
Uncooperative-ness	1.5±1.0	Health concerns	52.5±13.9	Total score	5.8±4.6
Emotional withdrawal	1.3±0.6	Bizarre mentation	57.3±10.1	Mean score	0.5±0.7
Suicidality	1.4±0.6	Anger	52.4±12.2	Delusions	0.1±0.2
Self-neglect	1.1±0.2	Cynicism	59.5±11.7	Hallucinations	0.0±0.0
Bizarre behaviour	1.2±0.3	Antisocial practices	54.3±11.0	Agitation/ aggression	0.2±0.6
Elevated mood	1.1±0.4	Type A	53.2±8.9	Depression/ dysphoria	2.2±2.3
Motor hyperactivity	1.2±0.3	Low self-esteem	54.5±13.4	Anxiety	0.5±1.0
Distractibility	1.2±0.1	Social discomfort	47.7±10.5	Elation/ euphoria	0.2±0.9
		Family problems	57.7±10.9	Apathy/ indifference	1.7±1.9

GOK (mean scores) (Ganzevles et al., 1994)			QUALIDEM (mean scores) (Oudman and Zwart, 2012)		EPI (mean percentile scores) (Plutchick and DiScipio, 1974)	
	K[a]	P[b]				
Observa-tion	5.6	5.1	Care relationship	55.2±21.9	Gregarious	69.3
ADL	5.8	4.8	Positive affect	70.0±22.4	Trustful	77.9
Memory	5.7	4.9	Negative affect	72.8±21.2	Poorly controlled	32.6
Planning	4.7	3.9	Restless tense behaviour	68.9±33.7	Timid	72.4
Social behaviour	5.0	4.3	Positive self- image	82.6±21.2	Depressed	48.6
Affect/ emotion	4.8	4.9	Social relations	63.3±23.3	Distrustful	28.5
(Alcoholic) dementia	7.0	6.9	Social isolation	69.9±20.4	Controlled	47.6
			Feeling at home	63.2±27.0	Aggressive	30.2
			Have some-thing to do	55.1±33.8	Bias	74.4

Table 4. Continued

Reported Severity (score ± SD)					
BPRS-E (mean scores) (Blansjaar et al., 1992)		**MMPI-2 (mean T-scores or percentile scores) (Egger et al., 2002)**		**NPI* (mean scores) (Cheon et al., 2008)**	
		Work inter-ference	53.5±11.0	Disinhibition	0.3±0.7
		Negative treatment indicators	53.6±11.7	Irritability/ lability	0.7±1.3
				Aberrant motor behaviour	0.0±0.0
BPRS (Cheon et al., 2008)				Sleep/night-time behaviour	0.0±0.0
Total score T0*	42.2±5.1			Appetite/eating disorders	0.0±0.0
Total score T1**	35.5±4.9				
Scores each item are not given					

Abbreviations:
BPRS (-E) = Brief Psychiatric Rating Scale (-Expanded): 18-24 items on psychiatric symptoms, ranging 1 "not present" to 7 "extremely severe". Score ≥4 = pathologic. Total score 24-168.
MMPI-2 = Minnesota Multiphasic Personality Inventory-2: a variety of scales with a total of 567 items on personality and psychopathology. Individual scores (=T-score) together represent a profile. T-score 40-59 = the mean, T-score ≥ 60 = pathologic.
NPI = Neuropsychiatric Inventory: 12 domains on behaviour symptoms. Frequency (ranging 1 "rarely" to 4 "very often"), severity (ranging 1 "mild" to 3 "severe") and total score (frequency x severity) can be calculated of each individual symptom. Total score ≥4 indicates the presence of a clinically relevant symptom. Total NPI score 0-144. Possible, the author has recoded the scoring.
GOK = Behaviour Observation Scale for patients with KS: a Dutch, non-validated instrument, that has been used once with 7 subscales and a total of 118 items on behaviour. Max score on subscale = 7 indicating less problem behaviour.
QUALIDEM = Dementia specific quality of life instrument: 9 subscales with a total of 37 items (item ranging 0 "never" to 3 "often"). Scores are linearly transformed from 0 to 100 by the author, higher scores indicate a better quality of life.
EPI =Emotions Profile Index: 8 subscales representing personality traits with a total of 62 items. Mean percentile scores are given. Fiftieth percentile represents the average score for the EPI standardization group (normal population).
*Baseline tests.
**After 12-week treatment with memantine.
[a]Specialised Korsakoff ward in psychiatric hospital.
[b]General ward in psychiatric hospital.

	GOK (mean scores) (Ganzevles et al., 1994)		QUALIDEM (mean scores) (Oudman and Zwart, 2012)	EPI (mean percentile scores) (Plutchick and DiScipio, 1974)
	K[a]	P[b]		

DISCUSSION

This is the first systematic review of the literature to examine behavioural symptoms in patients with KS. A total of 15 studies reporting on a variety of symptoms were included. Prevalence estimates varied widely across studies. Severity estimates were more consistent and all below pathological thresholds. Because the studies had serious methodological limitations and were very heterogeneous, these results have to be interpreted with caution.

Main findings and interpretation

Low quality and heterogeneity of the included studies

According to guidelines to assess the methodological quality of prevalence studies, the included studies scored poorly on almost all criteria. None of the studies were primarily designed to estimate the prevalence or severity of behavioural symptoms. With regard to the prevalence estimates, the occurrence of behavioural symptoms was mostly reported as a comorbid condition and obtained clinically. The definition of these conditions was often not reported and terms varied from diagnoses based on psychiatric nosology to clinical symptoms across studies. Also, the time period during which the prevalence of the behavioural symptoms was measured was often unknown or differed widely across studies. Regarding the severity estimates, a wide variety of assessment instruments was used. Most studies did not provide information on the validity and reliability of the used assessment instruments.

Besides the poor methodological quality, study heterogeneity hindered pooling and interpretation of the data. Most studies involved small, selective samples, which differed widely across studies with respect to many features. For example, a wide variety of definitions of KS and other alcohol-related cognitive disorders was used, based on different classification systems. Also, patients were included from different settings and during different stages of their disease.

Furthermore, inclusion criteria varied across studies. The alcohol abstinence period before subjects were assessed varied or was not reported. Certain alcoholrelated cognitive impairment is reversible with abstinence (Gupta and Warner, 2008), and the alcohol abstinence period that is required before KS or other alcohol-related cognitive disorders can be diagnosed has to be at least 6 weeks (Walvoort et al., 2013). When measured in the initial stage of the illness, symptoms like hallucinations, agitation or anxiety could also be attributed to alcohol withdrawal

delirium or the acute Wernicke phase (Wijnia et al., 2012). This could have resulted in an overestimation of the prevalence and severity.

In some studies, patients were excluded based on their age. For example, in the study of Draper (Draper et al., 2011), patients were excluded below the age of 50 years, while KS can also appear in this age group. The effect of age on behavioural symptoms in KS patients is unclear. Other studies excluded patients in the presence of active psychotic symptoms, which may lead to underestimation of rates.

Lastly, about half of the studies were on KS patients in institutionalized settings from the Netherlands, which has a long-standing tradition of long-term care for KS patients in specialist Korsakoff wards. This could also influence the generalizability of the results.

Prevalence of behavioural symptoms

In view of the serious methodological limitations, results should be interpreted with caution. Based on the extracted data, depressive symptoms and disorders and agitation and aggression were most prevalent. This was followed by psychotic symptoms and disorders and anxiety and anxiety disorders. The wide range in rates of psychiatric disorders, and psychiatric and behavioural symptoms we found, is probably partly the result of the heterogeneity of the included studies.

Severity of behavioural symptoms

With regard to severity of the behavioural symptoms, scores were all below pathological thresholds. Scores on apathy were highest. The relatively low severity scores conflict with experiences from clinical practice, as reported by several previous studies amongst KS patients (Egger et al., 2002; Gerridzen and Goossensen, 2014; Ridley et al., 2013; Thomson et al., 2012; Victor et al., 1989). These authors and other professionals involved in the daily care of KS patients noticed from their own clinical experience that behavioural symptoms occur frequently and are difficult to manage. Gerridzen and Goossensen (2014) suggested an overuse of psychotropics to manage challenging behavioural symptoms such as agitation and aggression.

Most of the current knowledge on behavioural symptoms is based on dementia research (Brodaty et al., 2015; Zuidema et al., 2007). Behavioural symptoms in dementia often have serious adverse consequences and cause distress to both patients and their caregivers (Ornstein and Gaugler, 2012; Zwijsen et al., 2014). Moreover, challenging behavioural symptoms in dementia often contribute to institutionalization (Gaugler et al., 2009). Knowledge about behavioural

symptoms in dementia has been found important to understand and manage these symptoms. However, behavioural symptoms in KS are hardly studied yet and their consequences for caregivers are unclear. We hypothesize that a better insight in the type of behavioural symptoms that are particularly prevalent and severe in KS patients, could, for example, help care staff to determine which approach or intervention might work best, and ultimately may lower distress to patients and caregivers.

There are several reasons that could explain the discrepancy between the relatively low severity estimates found in our study and the experiences from clinical practice. First, care staff who completed the assessment instruments in most studies could have underestimated the severity of symptoms, because they might have become used to the challenging behaviours. In studies using self-report instruments completed by the patients, such as the MMPI-2 and EPI, the lack of insight into their disease might have resulted in low severity estimates. Lack of insight into disease is another typical characteristic of this patient group that is frequently observed in practice by care staff. Patients often do not have any care demands themselves and are reluctant to receive care, or as Egger states 'the patient believes that nothing is wrong with him' (Egger et al., 2002). Little has been reported on this feature in the included studies, but the two studies that did include items covering this domain presented relatively high scores (on the BPRS-E item 'grandiosity' and on the QUALIDEM subscale 'positive self image'), indicating an impairment in awareness of their disease (Blansjaar et al., 1992; Oudman and Zwart, 2012). Egger et al. (2002) found differences between the severity ratings of care staff and patients for some behavioural symptoms. These findings suggest that lack of insight into the disease affects behaviour in KS patients.

Impaired awareness, or lack of insight into the disease, can be observed in a wide variety of neuropsychiatric disorders (Prigatano, 2014). From research in dementia, it is known that impaired awareness is associated with behavioural symptoms and caregiver burden (Aalten et al., 2006; Starkstein et al., 2010; Turró-Garriga et al., 2013). To the best of our knowledge, the association between impaired awareness and behavioural symptoms in KS patients has not been studied yet. Furthermore, the studies included were not primarily designed to assess behaviour. Therefore, it is possible that the used assessment instruments did not correctly detect behavioural symptoms.

Next, most patients in the included studies were admitted to specialist psychiatric hospitals or LTCFs, which provide intensive support and structure to patients.

Dutch care staff has experienced that these specialist wards seem to have a positive effect on the behaviour of KS patients (Ganzevles et al., 1994; Kopelman et al., 2009; Schepers et al., 2000).

Finally, it could have been possible that the use of psychotropics has influenced the severity of symptoms. On the one hand, psychotropics can mask emotional functioning and therefore have lowered estimates. On the other hand, these drugs could have increased certain symptoms, such as apathy due to side-effects (Zuidema et al., 2006).

Strengths and limitations

This is the first systematic review of the literature on behavioural symptoms in patients with KS. Our review has several strengths. Recommended guidelines from the PRISMA statement were carefully followed. An extensive search strategy was used to identify relevant studies in multiple electronic databases. Two reviewers independently selected the studies and extracted their data. Finally, the methodological quality of included studies was assessed with existing guidelines.

Limitations of this review are related to the poor quality and heterogeneity of the included studies. We provided only medians and ranges of the estimates. As no high-quality observational studies could be identified, we were limited in drawing conclusions about the prevalence and severity of behavioural symptoms in KS patients.

Directions for future research

High-quality observational studies designed to study the prevalence and severity of behavioural symptoms in KS patients are warranted to develop a better insight. The results of our review indicate that defining a target population clearly will be a challenge given the diagnostic difficulties and the heterogeneity of alcohol-related cognitive disorders. Therefore, consensus on diagnostic criteria for KS is strongly recommended. Furthermore, future studies should use an abstinence period of at least 6weeks before the diagnosis of KS is assessed.

To increase the generalizability of findings, efforts should be made to recruit a sufficiently sized and heterogeneous sample of KS patients. KS patients can be recruited from a variety of settings such as psychiatric hospitals, assisted living facilities and nursing homes.

Furthermore, to study behavioural symptoms in KS patients, established, reliable and validated assessment instruments, such as the NPI, should be used. As lack of insight into the disease may underlie behavioural symptoms, it would be interesting if future studies cover this domain in their measurement instruments to enable a better insight in this relationship.

CONCLUSION

The studies included in this review provide some indication that various behavioural symptoms occur — sometimes very frequently — in KS patients. Good quality studies are needed to acquire reliable estimates of the prevalence and severity of behavioural symptoms in KS. This could improve understanding and managing behavioural symptoms in patients with KS and help both informal and professional caregivers to better support the needs of this specific patient group.

APPENDIX I: SEARCH STRATEGY PUBMED (MEDLINE)

Method: #6 AND #7=#8

Korsakoff syndrome
(#1 OR #2=#6)

#1 Korsakoff (*mesh terms*):
"korsakoff syndrome"[mesh] OR "alcohol amnestic disorder"[mesh] OR "wernicke encephalopathy"[mesh]

#2 Korsakoff (*tiab or ot*):
korsako*[tiab] OR korsako*[ot] OR alcohol amnestic disorder*[tiab] OR alcohol amnestic disorder*[ot] OR wernicke encephalopath*[tiab] OR wernicke encephalopath*[ot] OR wernicke-korsako*[tiab] OR wernicke-korsako*[ot]

Behavioural symptoms
(#3 OR #4 OR #5=#7)

#3 behavioural symptoms (*mesh terms*):
"affect"[mesh] OR "affective symptoms"[mesh] OR "aggression"[mesh] OR "apathy"[mesh] OR"awareness"[mesh] OR "anxiety disorders"[mesh] OR "anxiety"[mesh] OR "behaviour"[mesh] OR "behav- ioural symptoms"[mesh] OR "delusions"[mesh] OR "depression"[mesh] OR "depressive disorder"[mesh] OR "eating disorders"[mesh] OR "emotions"[mesh] OR "euphoria"[mesh] OR "executive function" [mesh] OR "hallucinations"[mesh] OR "irritable mood"[mesh] OR "mood disorders"[mesh] OR "negativism"[mesh] OR "neuropsychology"[mesh] OR "neuropsychiatry"[mesh] OR "obsessive compulsive disorder"[mesh] OR "obsessive hoarding"[mesh] OR "personality"[mesh] OR "personality disorders" [mesh] OR "psychiatry"[mesh] OR "psychomotor agitation"[mesh] OR "psychotic disorders"[mesh] OR "sexual behaviour"[mesh] OR "sleep disorders"[mesh] OR "wandering behaviour"[mesh]

#4 behavioural symptoms [*tiab*] *or* [*ot*] (*mesh terms*):
affect[tiab] OR affect[ot] OR affective sympt*[tiab] OR affective sympt*[ot] OR aggression[tiab] OR aggression[ot] OR apathy[tiab] OR apathy[ot] OR awareness[tiab] OR awareness[ot] OR anxiety disorder*[tiab] OR anxiety disorder*[ot] OR anxiety[tiab] OR anxiety[ot] OR behav*[tiab] OR behav*[ot] OR behavioural sympt*[tiab] OR behav- ioural sympt*[ot] OR behavioural

sympt*[tiab] OR behavioural sympt*[ot] OR delusion*[tiab] OR delusion*[ot] OR depress*[tiab] OR depress*[ot] OR depressive disorder*[tiab] OR depressive disor- der*[ot] OR eating disorder*[tiab] OR eating disorder*[ot] OR emotion*[tiab] OR emotion*[ot] OR euphoria[tiab] OR euphoria[ot] OR executive funct*[tiab] OR executive funct*[ot] OR hallucination*[tiab] OR hallucination*[ot] OR irritable mood[tiab] OR irritable mood[ot] OR mood disorder*[tiab] OR mood disorder*[ot] OR negativism[tiab] OR negativism[ot] OR neuropsychol*[tiab] OR neuropsychol*[ot] OR neuropsychia*[tiab] OR neuropsychia*[ot] OR obsessive compulsive disorder* [tiab] OR obsessive compulsive disorder*[ot] OR ob- sessive hoarding[tiab] OR obsessive hoarding[ot] OR personality[tiab] OR personality[ot] OR personality disorder*[tiab] OR personality disorder*[ot] OR psychia*[tiab] OR psychia*[ot] OR psychomotor agitation[tiab] OR psychomotor agitation[ot] OR psychotic disorder*[tiab] OR psychotic disorder*[ot] OR sexual behav*[tiab] OR sexual behav*[ot] OR sleep disorder*[tiab] OR sleep disorder*[ot] OR wandering behav*[tiab] OR wandering behav*[ot]

#5 behavioural symptoms [tiab] or [ot] (free text words):
affective disorder*[tiab] OR affective disorder*[ot] OR agitation[tiab] OR agitation[ot] OR aggressive behav* [tiab] OR aggressive behav*[ot] OR anosognosia[tiab] OR anosognosia[ot] OR behaviour disinhibition[tiab] OR behaviour disinhibition[ot] OR behaviour disinhibition[tiab] OR behaviour disinhibition[ot] OR behaviour probl*[tiab] OR behaviour probl*[ot] OR behaviour probl*[tiab] OR behaviour probl*[ot) OR behaviour disorder*[tiab] OR behaviour disorder*[ot] OR behaviour disorder*[tiab] OR behaviour disorder*[ot] OR behaviour sympt*[tiab] OR behaviour sympt*[ot] OR behaviour sympt*[tiab] OR behaviour sympt*[ot] OR disinhi- bition[tiab] OR disinhibition[ot] OR eating disturban*[tiab] OR eating disturban*[ot] OR emotional disturb*[tiab] OR emotional disturb*[ot] OR hoarding[tiab] OR hoarding[ot] OR hoarding behav*[tiab] OR hoarding behav*[ot] OR impulsiveness[tiab] OR impulsiveness[ot] OR irritability[tiab] OR irritability[ot] OR neuropsychiatric sympt*[tiab] OR neuropsychiatric sympt*[ot] OR psychiatric sympt*[tiab] OR psychiatric sympt*[ot] OR psycho- logic sympt*[tiab] OR psychologic sympt*[ot] OR psychosexual behav*[tiab] OR psychosexual behav*[ot] OR psychosis[tiab] OR psychosis[ot] OR psychotic sympt*[tiab] OR psychotic sympt*[ot] OR repetition [tiab] OR repetition[ot] OR repetitive behav*[tiab] OR repetitive behav*[ot] OR restlessness[tiab] OR restlessness[ot] OR screaming[tiab] OR screaming [ot] OR sexual disinhibition[tiab] OR sexual disinhibition[ot] OR sexual dysfunct*[tiab] OR sexual dysfunct*[ot] OR sleep disturb*[tiab] OR sleep disturb*[ot] OR wandering[tiab] OR wandering[ot]

APPENDIX II: BOYLE'S GUIDELINES FOR EVALUATING PREVALENCE STUDIES (BOYLE, 1998)

Sampling:

1. Was the target population clearly defined?
2. Was probability sampling used to identify potential respondents?
3. Did characteristics of respondents match the target population?

Measurement:

4. Were the data collection methods of behavioural symptoms standardized?
5. Was the measure of behavioural symptoms reliable?
6. Was the measure of behavioural symptoms valid?

Analysis:

7. Were special features of sampling design accounted for in the analysis?
8. Did the reports include confidence intervals for statistical estimates?

Chapter 3

Executive dysfunction in patients with Korsakoff's syndrome: a theory-driven approach

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Egger, J. I. M., & Kessels, R. P. C. (2018). Executive dysfunction in patients with Korsakoff's syndrome: A theory-driven approach. *Alcohol & Alcoholism, 54*(1), 23–29. https://doi.org/10.1093/alcalc/agy078

SUMMARY

Objective

In addition to amnesia, executive deficits are prominent in Korsakoff's syndrome (KS), yet poorly studied. This study investigates the degree of executive dysfunction in patients with KS for the three main executive subcomponents shifting, updating and inhibition using novel, theorydriven paradigms.

Methods

Executive functions were measured with six carefully designed tasks in 36 abstinent patients with KS (mean age 62.3; 28% woman) and compared with 30 healthy non-alcoholic controls (mean age 61.8; 40% woman). ANOVAs were conducted to examine group differences and effect sizes were calculated.

Results

Compared to healthy controls, patients with KS were impaired on the executive subcomponents shifting and updating. No statistically significant group difference was found on the factor inhibition.

Conclusions

Executive dysfunction in long-abstinent patients with alcoholic KS shows a profile in which shifting and updating ability are affected most. It also highlights that executive dysfunction is an important feature of KS and requires more attention in scientific and clinical practice, as these deficits may also affect daily functioning.

INTRODUCTION

Korsakoff's syndrome (KS) is a neuropsychiatric disorder, characterized by severe cognitive and behavioural deficits. It is caused by thiamine deficiency, most commonly associated witch chronic alcohol use (Bowden et al., 1994; Kopelman et al., 2009; Arts et al., 2017). Many patients have somatic as well as psychiatric comorbidity, use one or more psychotropic drugs and show neuropsychiatric symptoms which include depressive symptoms, agitation and aggression (Gerridzen et al., 2017). Other symptoms of KS include confabulations, apathy, disorders of affect, social-cognitive problems and impaired awareness (Arts et al., 2017; Rensen et al., 2017; Gerridzen et al., 2018). The cognitive deficits of patients with KS include severe anterograde and retrograde amnesia and executive dysfunction. Patients with KS suffer from profound contextual deficits in both working memory and episodic memory, while implicit memory is usually preserved (Kopelman et al., 2009; Kessels & Kopelman, 2012; Oudman et al., 2015; El Haj & Nandrino, 2017).

The DSM-5 classifies KS as 'alcohol-induced major neurocognitive disorder, amnestic confabulatory type' (American Psychiatric Association, 2013). Although this classification highlights the memory problems, executive dysfunction has been put forward as another prominent symptom of the syndrome (Van Oort & Kessels, 2009). Executive functions are cognitive processes responsible for controlling and regulation thoughts, emotions and behaviour. They are crucial for just about every aspect of life, including mental and physical health, school and vocational success and quality of life (Diamond, 2013) and closely related to the concept of fluid intelligence (i.e. reasoning; Van Aken et al., 2016). Typically, executive functions are often referred to as higher-order functions, such as planning, reasoning and problem solving, that are poorly defined as cognitive constructs. However, recent theories and models on executive function identified several 'core executive processes' that underlie these higher-order cognitive functions (Diamond, 2013). Three core executive components have been identified in previous research, namely inhibitory control (inhibition), working memory (updating) and shifting or cognitive flexibility (shifting) (Miyake & Friedman, 2012; Baggata & Alexander, 2016).

Executive dysfunction is consistently reported in KS patients (see, e.g. Van Oort & Kessels, 2009; Oscar-Berman, 2012; Maharasingam et al., 2013). For instance, patients with KS show deficits which include poor judgement and planning abilities (Oscar-Berman, 2012), and are found to be impaired on neuropsychological measures of executive function (e.g. the Behavioural Assessment of the Dysexecutive Syndrome [BADS]) (Maharasingam et al., 2013). Also, impairments in all three aforementioned

core components have been reported. For instance, Oscar-Berman et al. (2004) used the Wisconsin Card Sorting Test to measure executive dysfunction in patients with alcoholic KS, alcoholics without KS and healthy controls and found that patients with KS performed worse than alcoholics on perseverative errors, reflecting poor shifting ability (Miyake et al., 2000; Kessels et al., 2008). Furthermore, patients with KS demonstrate impairments on working memory tasks, reflecting the factor updating (Hildebrandt et al., 2004; Van Geldorp et al., 2012). As for the factor inhibition, results are less consistent. For example, deficits in oculomotor inhibition (Van der Stigchel et al., 2012), and impaired performance on the Stroop Colour-Word Test (El Haj et al., 2017; El Haj & Nandrino, 2018) have been reported in KS. However, Pollux et al. (1995) concluded that patients with KS are in fact able to inhibit the dominant response in a random-number generation task that requires executive control. Furthermore, Pitel et al. (2008) found impaired inhibition in KS, but to a lesser extent than shifting and updating deficits.

Brion et al. (2014) reviewed the existing research on executive dysfunction in KS and concluded that an accurate overview of specific executive deficits in KS is lacking, as most investigations used multifaceted executive tasks covering multiple cognitive processes. This problem is also known as the task impurity problem (Packwood et al., 2011), meaning that EF tasks assess multiple executive subcomponents and that non-executive processes, such as language or motor speed, affect results on these tasks as well (Snyder et al., 2015). Therefore, executive dysfunction should be studied using more targeted and precise executive paradigms in clinical research. This study aims to directly compare and quantify impairments of each executive subcomponent of patients with KS. Using six carefully designed tasks as measures of shifting, updating and inhibition, more targeted assessment of these subcomponents is possible, and ceiling and floor effects are prevented. KS performance will be compared to a matched healthy control group.

METHODS

Participants

Two groups of participants took part in this study. The first consisted of 36 patients with alcoholic KS. Thirty of these were inpatients of Atlant Korsakov centre of expertise, a specialized nursing home for Korsakoff patients in Beekbergen, the Netherlands. Six patients were in-patients of the Korsakoff Clinic of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. All patients were in the chronic stage of Wernicke–Korsakoff syndrome. Median duration of alcohol

abstinence was 6.6 years (range 0.42–16 years). Patients were selected for the study if they (a) fulfilled the DSM-5 criteria for substance/medication-induced major neurocognitive disorder and the clinical criteria of KS described by Kopelman (2002), (b) had no additional cognitive deficits (e.g. tumour, stroke) as followed from the medical charts, (c) had an estimated IQ score above 75 and (d) were aged <70, to make sure none fulfilled the criteria for alcohol-related dementia (Oslin et al., 1998). The second group consisted of 30 healthy controls (patient relatives, volunteers or employees of nursing home Atlant). None of the healthy controls used psychotropic medication and none of them were heavy drinkers, as indicated through the Five-Shot questionnaire (Seppäet al., 1998), a short questionnaire on which a score of 2.5 or higher indicates possible alcohol misuse (max = 7).

Table 1 presents the demographic data of both groups. Education level was assessed using seven categories, in accordance with the Dutch educational system: 1 being the lowest (less than primary school) and 7 the highest (academic degree). Intelligence was estimated using the Dutch version of the National Adult Reading Test (NART; Schmand et al., 1992). General cognitive functioning was measured with the Dutch version of the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) that has been validated in patients with alcohol-related cognitive impairment (Bruijnen et al., 2018). Controls were excluded when they scored below 24 on the MoCA. In order to create matched groups, only healthy controls between 50 and 70 years were recruited. The study was approved by the Ethics Committee of the Faculty of Social Sciences of Radboud University (Ref. no. ECSW2015-1210-343) and the institutional review boards of Korsakoff Centre Atlant (Ref. no. mdz/mp/2015-005) and Vincent van Gogh Institute for Psychiatry (CWOP; Ref. no. 15.04365). Written informed consent was obtained by all participants. When patients were not legally competent, their legal representative also signed the informed consent form.

Table 1. Demographic data for patients with Korsakoff's syndrome and healthy controls

	Korsakoff's syndrome (*n* = 36)	**Healthy controls (*n* = 30)**
Age *M (SD)*	62.3 (5.3)	61.8 (5.6)
Sex distribution (% woman)	27.8	40.0
Education level *Median*	4.0	5.0
Estimated IQ (NART) *M (SD)*	99.9 (16.1)	104.8 (15.5)
MoCA – executive part** *M (SD)*	3.2 (1.3)	4.1 (0.8)
MoCA – nonexecutive part** *M (SD)*	15.3 (3.0)	22.3 (1.7)

Note. No statistically significant differences between the groups were found on age, sex distribution, education level or IQ score.
NART = National Adult Reading Task (Dutch Version)
MoCA = Montreal Cognitive Assessment
** p <.05; **p* ≤.001

Instruments

Six novel experimental executive function tasks were developed, two tasks for each executive subcomponent. These tasks were based on the ones described by Friedman et al. (2008), but adapted for use in cognitively impaired patients. The tasks were programmed in PsychoPy version 1.83.03 (Peirce, 2007) on a research laptop (Dell XPS M1530) with a 15-inch screen and using Windows 7. A tailor-made button box was used to measure reaction time (RT) with millisecond accuracy. The order of the tests was counterbalanced and all tasks were extensively piloted and modified if necessary, making sure the length and complexity made administration in cognitively impaired individuals feasible, yet avoiding ceiling performance in cognitively unimpaired individuals. Figure 1 shows a schematic overview of each task.

Shifting

To measure shifting, the Category Switch Task and the Number – Letter Switch Task were used. In the Category Switch Task participants had to (1) categorize words as either living (left button) or nonliving (right button) when a heart was presented and (2) whether the object was larger (left button) or smaller (right button) than a soccer ball when a soccer ball was presented. During the task the category cues remained visible on the screen. In the Number–Letter Switch Task a letter-number or a number–letter pair (e.g. 4G, K3) was presented above or below a line. Participants had to indicate (1) whether the number was even (left button) or odd (right button) when the pair was above the line and (2) whether the letter was a vowel (left button) or a consonant (right button) when the pair was below the line. Again, the cues remained visible throughout the task. Both tasks consisted of two blocks of

24 switch and 24 no-switch trials. A trial was considered a switch trial when the cue differed from the trial before (e.g. the pair changed from above to below the line). Both blocks were preceded by six practice trials and the tests started with one practice block of 24 trials. Switch cost was used as outcome measure, calculated as the difference between the median RT of the switch trials and the median RT of the no-switch trials.

Updating

The Spatial 2-Back Task and the Letter Memory Task measured working memory/updating. The Spatial 2-Back consisted of 10 squares, placed in a circle. After a tone, one box flashed black for 500 ms, after which participants had to respond by answering the question 'Was this the same box as two flashes earlier?' with 'yes' (left button) or 'no' (right button). Two blocks of 24 trials were preceded by a 24-trial practice block. The percentage of correct answers was selected as outcome measure. The instruction remained visible on the screen during the task. In the Letter Memory Task participants were instructed to recall the last two letters of a series of letters that were each presented for 2500 ms. After each letter, the participant was instructed to verbally rehearse the last two letters they had seen by mentally adding the most recent letter and 'forgetting' the third letter back. The task started with three practice trials consisting of five, seven and nine letters and was followed by nine trials of each length. Outcome measure was the percentage correct answers.

Inhibition

Inhibition was measured using the Antisaccade Task and the Stop Signal Task. In the Antisaccade Task participants had to fixate on a fixation point for a variable amount of time (1.500–3.500 ms). A black square (22 × 22 mm2) was briefly presented on one side of the fixation point (for 150 ms), followed by a an arrow (16 mm) inside an open square on the opposite side for 175 ms. After that, the arrow was masked with a grey square. The instruction was to indicate whether the arrow was directed to the left (left button) or the right (right button). A total of 54 trials were preceded by 18 practice trials. The percentage correct was included for analyses. During the Stop Signal Task participants, the ongoing task was to categorize words as either an animal (left button) or a non-animal (right button). During the target trials, however, participants were instructed not to respond when they heard a 100-ms long tone. This signal was present in 25% of the trials on one of the three possible moments: 50 of 225 ms before the individual's average RT, or 50 ms after the onset of the trial. The task started with 48 practice trials, followed by a 48-trial block used to calculate each participant's average RT. Two blocks of 48 target trials were

preceded by 12 practice trials. Outcome measure was the stop-signal RT, calculated following Friedman et al. (2008): for each delay the probability of responding was calculated (a number between 0 and 1). Second, the correct no-signal go trials were rank ordered. For each delay the nth RT of this row was selected, with n being the number of the correct no-signal go trials, multiplied by the probability of responding of each delay. The stop-signal delay was subtracted from this nth RT. Last, the stop-signal RTs for all delays were averaged.

Procedure

Patients completed the neuropsychological testing at the centre were they stayed, in a quiet room and with a trained researcher. All controls were tested at nursing home Atlant. All participants completed the MoCA and the NART prior to the assessment of the executive tasks. The total testing session lasted ~1–1.5 h.

Analyses

Results were analysed using the Statistical Package for the Social Sciences (SPSS) Version 25. For all RT measures, RTs of errors and trials following errors were not used in the analysis. All RTs are in milliseconds. Skewness and kurtosis scores were determined for all dependent variables to check for normality. For each tasks it was calculated whether patients and controls performed above chance level and whether floor- or ceiling effects occurred. For each executive subcomponent a compound score was calculated by averaging the Z-scores of the two tasks per subcomponent. The directionality of the Z-scores of the two Shifting Tasks and the Stop Signal Task were reversed so that higher scores indicated better performance. ANOVAs were performed to calculate group differences and effect size was calculated using Cohen's d.

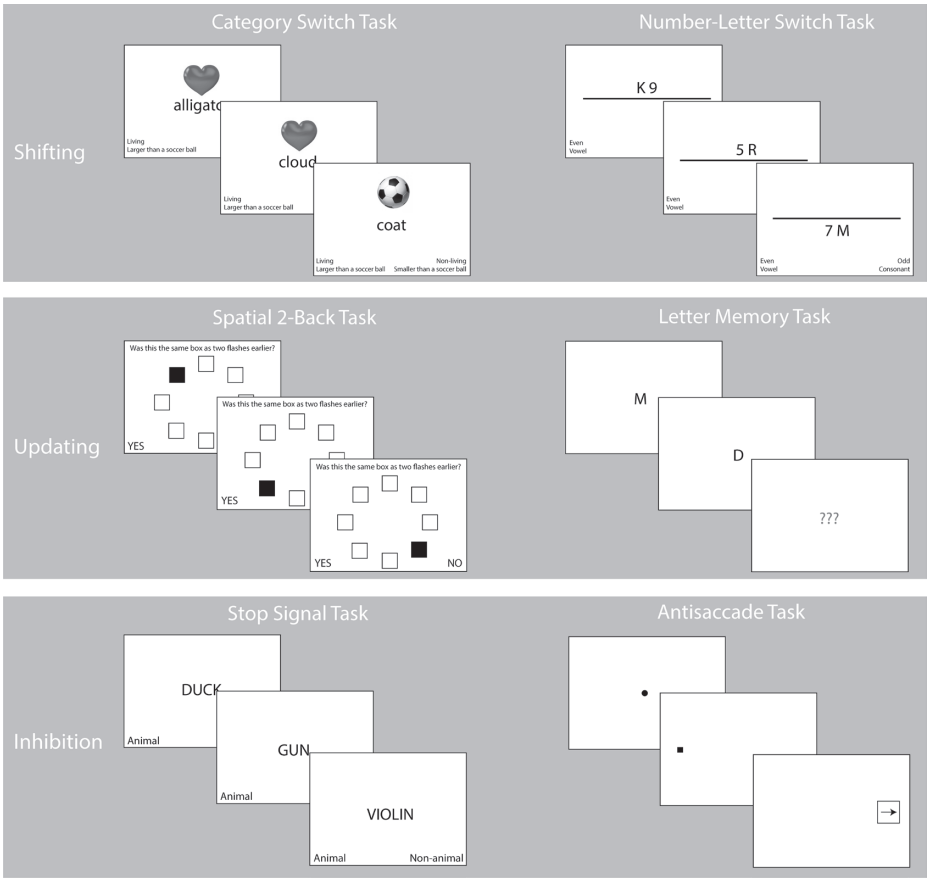

Figure 1. Schematic overview of the paradigms tapping the three executive domains *shifting, updating* and *inhibition*. In the *Category Switch Task,* participants had to categorize words in as either a (1) living or nonliving object when a heart was presented on the screen and (2) whether the object was smaller or larger than a soccer ball when a soccer ball was presented on the screen. In the *Number Letter Switch Task,* participants had to indicate (1) whether the number was odd or even when the pair was above the line and (2) whether the letter was a consonant or a vowel when the pair was below the line. In the *Spatial 2-Back Task*, participant had to respond by answering the question "Was this the same box as two flashes earlier?" with "yes" (left button) or "no" (right button). In the *Letter Memory Task,* they were instructed to recall the last two letters of a series letters who were presented on the screen for 2,500 ms per letter by adding the most recent letter and dropping the third letter back. In the *Stop Signal Task*, participants had to categorize words into an animal or a non-animal, but when they heard a signal (a 100-ms long tone) participants were instructed to not respond. Finally, in the *Antisaccade Task*, participants had to fixate on a point. A black square was briefly presented on one side of the fixation point, followed by an arrow inside an open square on the opposite side, which was masked with a grey square after 175 ms. Participants had to indicate whether the arrow was directed to left or right.

RESULTS

All patients with KS were able to comprehend the instructions and complete the tasks. In two patients, the data of one task (Stop Signal Task or Spatial 2-Back Task) were missing due to apparatus failure. Figure 2 shows the executive compound scores for the two groups. Patients with KS performed significantly worse than controls on shifting ($F(1,64) = 27.4$; $P < 0.0005$; Cohen's $d = 1.35$) and updating ability ($F(1,63) = 20.1$; $P < 0.0005$; Cohen's $d = 1.14$) than healthy controls. No significant difference was found between the patients with KS and the controls on inhibition ability ($F(1,63) = 3.5$; $P = 0.066$). The scores on each task will be discussed in the next sections for patients and controls (Table 2).

Shifting

Both patients with KS and controls performed above change level on both shifting tasks (all t-values >17.1, all $P < 0.0005$). Patients demonstrated significantly higher switch cost than healthy controls both on the Category Switch Task ($F(1,64) = 13.7$, $P < 0.0005$) and on the Number Letter Switch Task ($F(1,64) = 24.7$, $P < 0.0005$).

Updating

For the Spatial 2-Back Task, both patients and controls performed above change level (t-values > 2.5; $P < 0.05$). For the Letter Memory task, no change performance could be computed, as this is a free recall task. Patients were significantly less accurate than controls on the Spatial 2-Back task ($F(1,63) = 6.3$; $P < 0.05$). The scores on the Letter Memory Task were non-normally distributed. All scores were square-transformed, after which the normality assumption was met (skewness = −1.48, SE = 0.26; kurtosis = 0.96, SE = 0.51). Patients were significantly less accurate on the Letter Memory Task ($F(1,64) = 20.8$; $P < 0.0005$) compared to controls.

Inhibition

For both the Antisaccade and the Stop Signal Task, mean scores were significantly above change level for patients and controls (t-values > 18.14, $P < 0.0005$). No differences were found between KS patients and healthy controls in accuracy on the Antisaccade Task ($F(1,64) = 1.1$; $P = 0.294$). On the Stop Signal Task, no between-group difference on the Stop Signal RT measure ($F(1,63) = 3.4$; $P = 0.071$). A closer look at the RTs of the latter task shows that patients ($M = 812.7$; $SD = 107.7$) were significant slower than healthy controls ($M = 685.9$; $SD = 58.1$) on the RT block (the first 48 trials) that was used to determine each participant's average RT ($F(1,63) = 33.2$; $P < 0.0005$), but no significant difference was found between patients ($M = 892.4$; $SD = 110.6$) and healthy controls ($M = 923.7$; $SD = 124.7$) when the

RT was calculated as the median RT of all trials (F(1,63) = 1.2; P = 0.287). Patients (M = 67.3; SD = 8.7) were significantly less accurate on the task (F(1,63) = 26.3; P < 0.0005) than controls (M = 54.7; SD = 18.9)

Table 2. Performance on the individual executive tasks for the Korsakoff patients and the healthy controls

	Korsakoff's syndrome (*n* = 36) *M* (*SD*)	**Healthy controls (*n* = 30)** *M* (*SD*)	***p*-value**	**Cohen's *d***
Shifting				
Category switch				
Switch cost (ms)	1297.5 (1299.3)	391.0 (363.6)	<.0005	0.95
Number letter switch				
Switch cost (ms)	1758.7 (1180.8)	520.5 (283.9)	<.0005	1.44
Updating				
Spatial 2-Back*				
Accuracy (% correct)	56.6 (15.9)	66.0 (14.0)	<.05	0.63
Letter Memory**				
Accuracy (% correct)	77.4 (28.5)	98.4 (2.6)	<.0005	1.18
Inhibition				
Antisaccade				
Accuracy (% correct)	75.6 (8.4)	77.6 (7.2)	.294	0.26
Stop Signal*				
Stop signal RT (ms)	541.9 (144.4)	462.6 (202.3)	.071	0.45

*Missing data for one patient.

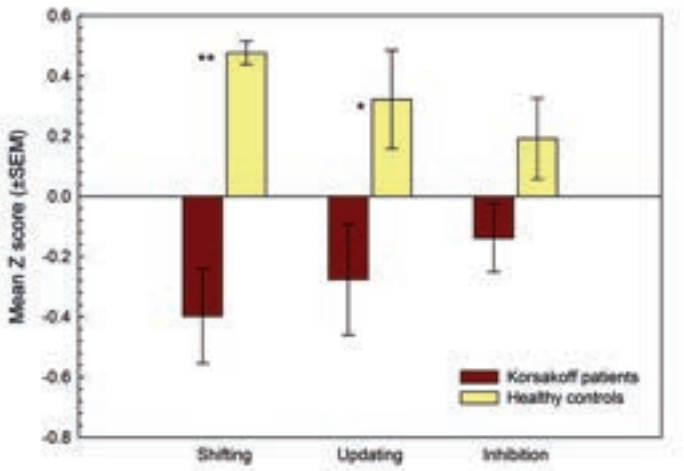

Figure 2. Executive compound scores per group. **p <.0005

DISCUSSION

This study aims to directly compare and quantify executive impairments in patients with KS. The results show a profile of executive dysfunction in which shifting and updating ability are affected most, while no significant differences between patients with KS and healthy controls were found on inhibition ability.

The largest effect size was found for shifting ability (Cohen's d = 1.35). This is in line with earlier results where patients with KS demonstrate an impaired performance on Card Sorting tests (Oscar-Berman et al., 2004; Kessels et al., 2008). Friedman and Miyake (2017) argued that shifting ability reflects flexibility (i.e. replacing goals or task sets when necessary) and that this process is somewhat opposite to goal maintenance (important for inhibition ability). Strong goal representations take longer time to replace, thus showing a stability (inhibition)/flexibility (shifting) trade-off. In our study, this pattern is observed in patients with KS (i.e. impaired shifting yet unimpaired inhibition).

Updating ability was also impaired in patients with KS. This extends previous research on updating/working memory in KS (Hildebrandt et al., 2004). Although traditionally, memory impairments in KS were considered to reflect a long-term memory deficit only (Butters & Cermack, 1980), more recent studies also found evidence for impairments in working memory in amnesic patients, that is, the ability to maintain and update information held for a brief period of time, especially on working memory/updating tasks that require more cognitive resources (i.e. having a higher working memory load). For instance, Van Geldorp et al. (2012) found deficits in associative working memory and argued that long-term encoding processes—subserved by the diencephalic-hippocampal circuitry— already took place during working memory tasks. This also explains the discrepancy with other findings of unimpaired performance on standard tests of working memory (e.g. digit span tasks; see e.g. Kopelman, 1985; Kessels et al., 2008).

The current results suggest preserved inhibition in patients with KS. As stated before, previous findings on inhibition are inconsistent. Oculomotor inhibition has been found to be impaired (Van der Stigchel et al., 2012), while dominant response inhibition seems to be preserved at least in some studies (Pollux et al., 1995). Differences in task demands may underlie these discrepancies. For instance, the behavioural Antisaccade Task used in our study differed from the one used by Van der Stigchel et al. (2012) in which eye movements were actually measured. In their task, participants were instructed to make pro- or antisaccade eye movements

depending on the colour of the fixation cross. Because participants had to switch between these instructions, this task instruction also relied on the patients' shifting ability. Furthermore, patient groups differ with respect to abstinence, with patients in Van der Stigchel et al. (2012) being abstinent for 1–7 months, complicating the interpretation as cognitive recovery from alcohol use and withdrawal occurs in this period (Stavro et al., 2013).

To understand why results on inhibition ability in patients with KS show discrepancies, a closer look on the construct of inhibition is necessary. Following Friedman and Miyake (2004) inhibition ability should be considered as a multidimensional construct that can be subdivided into three different processes: that is, prepotent response inhibition, resistance to distractors, and resistance to proactive interference. According to Friedman and Miyake, the tasks used in our study are both measures of prepotent response inhibition. Brion et al. (2018) measured prepotent response inhibition and resistance to distractors in patients with KS and alcoholics and concluded that patients with KS predominantly show impaired resistance to distractors rather than impaired prepotent response inhibition. This is in line with results of Pollux et al. (1995) and current findings, but in contrast with results of El Haj et al. (2017) and El Haj and Nandrino (2018), who found impaired inhibition in KS measured with the Stroop Colour Word Test. However, it remains under debate whether the Stroop task can be considered as a measure for prepotent response inhibition (Khng & Lee, 2014). Other factors are likely to have influenced inhibitory performance, such as the amount of time allowed for completion of the task or difference between computerized paradigms versus paper-and-pencil tests (see Kessels, in press). Finally, inhibition deficits could depend on other variables, for instance severity of overall cognitive impairment or abstinence duration. Further investigation is needed to clarify these discrepancies in inhibition-related impairments in patients with KS, considering inhibition as a multidimensional construct.

The present study aimed to overcome some shortcomings of previous research. To date, no study on executive dysfunction in patients with KS had been published in which specific executive subcomponents were examined using sensitive tasks (cf. Brion et al., 2014). We used a theory-driven approach and our design enables to make a direct comparison between each executive subcomponent. Describing executive dysfunction in terms of the three executive subcomponents might help to understand the underlying mechanism involved in executive dysfunction (Snyder et al., 2015). Second, patients with KS were abstinent for a long time (on average more than 6 years). This is particularly important because executive

dysfunction of alcoholics has been found to remain present more than a year after abstinence (Stavro et al., 2013). A short abstinence period in patients with KS can thus influence the results, because recently detoxified alcoholics are found to have executive dysfunction as well (Brion et al., 2017). Third, in comparison with other studies, we have a relatively large sample of patients with well-defined KS due to our selection criteria.

This study also has some limitations that should be addressed. First, we modified the tasks suggested by Friedman et al. (2008) to enable reliable administration in patients with KS. While these adaptations prevented floor effects, ceiling performance was found for the Letter Memory Test in healthy controls. Despite this ceiling performance, we still found a large updating deficit in KS compared to controls, although the effect size may have been attenuated by the high performance of the control group. Further adaptations are thus needed in future research to increase the complexity of this task. Second, we cannot rule out that non-executive processes may have influenced the performance on our tasks. To overcome this, Brion et al. (2017) used a comparable design but added non-EF baseline conditions to measure non-executive processes and use subtraction to calculate the 'pure' EF component. Although this method has clear advantages, it also substantially increased the length of each task, thus making administration in patients with KS more difficult and burdensome. Finally, it could be argued that including a second control group of non-KS alcoholics might have been informative. However, while previous studies have employed such a design (comparing patients with KS to alcoholic controls), the duration of abstinence always differs greatly between these two groups. That is, our sample of patients with KS has been abstinent for years, a status which has also been verified as all patients resided in a care home in which a strict alcohol policy was maintained. In turn, the chronic alcoholics used in previous studies (Pitel et al., 2007; Brion et al., 2017) had been abstinent only for days to weeks at most, indicating that any cognitive deficit measured are likely the result of the effects of alcoholic encephalopathy, which is largely reversible (Arts et al., 2017). Also, the abstinence status cannot be fully substantiated in alcoholics in outpatient addiction care, making it possible that findings may also be confounded by acute withdrawal effects of alcohol.

In conclusion, executive dysfunction of patients with KS shows a profile in which shifting and updating ability are affected most. It also highlights that executive dysfunction is an important feature of KS and requires more attention in scientific and clinical practice, as these deficits also affect daily functioning.

Chapter 4

The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Rensen, Y. C. M., Egger, J. I. M., & Kessels, R. P. C. (2020). The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome. *The Clinical Neuropsychologist, 34*(4), 740–754. https://doi.org/10.1080/13854046.2020.1738554

SUMMARY

Objective

Patients with Korsakoff's syndrome (KS) show executive dysfunction and neuropsychiatric symptoms. This study investigates whether specific executive subcomponents (shifting, updating, and inhibition) predict variance in neuropsychiatric symptoms. We hypothesized that shifting deficits, in particular, are associated with neuropsychiatric symptoms.

Methods

Forty-seven patients participated (mean age 61.5; 11 women). Executive function (EF) was measured using six component-specific tasks. Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory – Questionnaire (NPI-Q). General cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA). First, factor analysis was conducted to examine shared variance across the EF tasks. Subsequently, a regression analysis was performed with the EF factors and the MoCA as predictors and the NPI-Q as the dependent variable. It was also investigated whether an interaction effect between the EF factors and the MoCA was present.

Results

The prevalence of neuropsychiatric symptoms was high (85.7% of the KS patients showed at least one symptom). A two-factor model was extracted with a shifting-specific factor and a combined updating/inhibition factor. The overall regression model was not significant, and no interaction was found between the EF factors and general cognitive functioning. However, a significant relationship between general cognitive functioning and neuropsychiatric symptoms (r = -.43; p <.01) was detected.

Conclusions

Results point at an association between neuropsychiatric symptoms and general cognitive functioning. Possibly, diminished cognitive differentiation in these patients with severe cognitive dysfunction accounts for the absence of a significant association between EF and neuropsychiatric symptoms. While the results should be interpreted with caution due to a limited sample size, the found association highlights the need to further unravel the underlying cognitive mechanisms of neuropsychiatric symptoms in patients with KS.

INTRODUCTION

Korsakoff's syndrome (KS) results from thiamine deficiency, mainly occurring in the context of chronic alcohol abuse and limited food intake (Nikolakaros et al., 2018; Wijnia et al., 2016), resulting in diencephalic lesions (notably in the mammillary bodies and thalamus; Harding et al., 2000). KS is characterized by chronic and severe cognitive impairments, including anterograde and retrograde amnesia and executive dysfunction. Other notable symptoms include neuropsychiatric symptoms, such as confabulations, apathy, irritability, agitation, aggression, or disinhibition (Arts et al., 2017; Gerridzen et al., 2017). A recent study examining neuropsychiatric symptoms in 281 patients with KS reported that 96.4% of the patients showed at least one neuropsychiatric symptom, with irritability/lability, agitation/aggression, and disinhibition being most prevalent (Gerridzen et al., 2018). Neuropsychiatric symptoms are associated with higher caregiver burden (Chen et al., 2017) and more frequent use of psychotropic drugs (Maust et al., 2017). In addition, patients with KS tend to overestimate their cognitive and functional capacities, typically having limited insight into their own disorder (Egger et al., 2002; Gerridzen et al., 2019), whilst also being institutionalized and dependent on daily care. This may explain the high prevalence of agitation/ aggression or disinhibition, as patients assume they do not need the provided care and may show frustration or aggression as a result. This challenging behavior might, in turn, be the reason for the extensively prescribed psychotropic drugs for managing neuropsychiatric symptoms, in addition to the cognitive deficits and comorbid psychiatric illnesses (Gerridzen & Goossensen, 2014).

There is evidence that neuropsychiatric symptoms may be related to executive dysfunction. For instance, in relatively small samples of patients with Alzheimer's disease, associations have been found between executive dysfunction and neuropsychiatric symptoms, especially agitation and disinhibition (Chen et al., 1998), as well as stereotypies and repetitive motor behavior (Gleichgerrcht et al., 2011). Apathy has also been repeatedly linked to executive dysfunction (Kawagoe et al., 2017; McPherson et al., 2002). Moreover, a proliferation of research emphasizes the relationship between executive dysfunction, behavioral impairments and psychopathology (Snyder et al., 2015), yet there is no general consensus on whether these are causally related.

There is abundant evidence that patients with KS show executive dysfunction (Brion et al., 2014; Maharasingam et al., 2013; van Oort & Kessels, 2009). Executive functions include higher-order processes such as planning, reasoning and problem-

solving, which are important for regulating our thoughts, emotions and behavior (Diamond, 2013). Typically, executive functioning is considered a multifaceted construct that can be subdivided into multiple components. Recent studies argue that 2 executive subcomponents can be distinguished within a unity/diversity model with a common executive function (common EF; previously described as an inhibition function) on the one hand, and an updating- and shifting-specific factor on the other (Baggetta & Alexander, 2016; Friedman & Miyake, 2017). The common EF variable reflects the ability to maintain and manage goals against all sort of distractors. This ability is measured with a range of inhibition tasks, in which goal maintenance is required. The shifting-specific function reflects the ability to replace goals when necessary, and the updating-specific factor reflects the ability to replace information in working memory whilst preserving some other, relevant information. Recently, patients with KS were found to be predominantly impaired on updating and shifting, while no deficits in inhibition were demonstrated (Moerman – van den Brink et al., 2019).

Studying executive functions in clinical and non-clinical samples is hampered by methodological issues such as the task impurity problem. That is, most (traditional) measures of executive functioning are non-specific in nature, tapping into multiple aspects of executive function as well as non-executive abilities, such as memory or motor speed (Kessels, 2019; Packwood et al., 2011; Snyder et al., 2015). A low score on an executive function test can thus be explained by either executive dysfunction itself or by deficits in non-executive abilities. To minimize the influence of non-executive abilities, Friedman (2016) recommended the use of multiple measures of executive functioning with extraction of the common variance in these tasks (by combining them into subdomain scores), thus resulting in a more reliable and valid measure of the 'pure' executive function.

To examine the relationship between neuropsychiatric symptoms and executive dysfunction in patients with KS, we propose a theory-driven approach, focusing on the three core executive subcomponents: shifting, updating and inhibition/common EF. These executive subcomponents will be measured with multiple, carefully designed, component-specific tasks of which latent variables will be composed to avoid the aforementioned problem of task-impurity. Previously we showed that KS patients were able to complete these tasks without floor effects (Moerman – van den Brink et al., 2019). We hypothesize a negative correlation between neuropsychiatric symptoms and the performance on executive measures. Previously we found shifting to be mostly affected in patients with KS (Moerman – van den Brink et al., 2019). Deficits in shifting ability may underlie perseverative

behavior, problems in dual-tasking, and adaptive behavior in general (Hatoum et al., 2018; Roberts et al., 2007), which are among the main symptoms of patients with KS (Arts et al., 2017; Gerridzen et al., 2017). We also hypothesize that shifting deficits will be the strongest predictor of neuropsychiatric symptoms.

METHODS

Participants

Forty-seven patients with KS participated in this study, see Table 1 for details. Thirty-seven of these were inpatients of the Korsakoff Centre of Expertise of Atlant, a specialized nursing home for Korsakoff patients in Beekbergen, the Netherlands. Ten of these were inpatients of the Centre of Excellence for Korsakoff and Alcohol-Related Cognitive Disorders of the Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. Data of 36 of the 47 patients were already available, as they had participated in our previous study, in which all executive tests and questionnaires were administered (with the executive task results reported in Moerman – van den Brink et al., 2019).

Patients were selected if they met the DSM-5 (American Psychiatric Association, 2013) criteria for alcohol-induced major neurocognitive disorder, amnestic confabulatory type (code: 291.1). Other inclusion criteria were: no additional neurological diagnosis or condition (e.g. stroke) as documented in the medical charts, and aged less than 70 to reduce the possibility that patients are also suffering from a neurodegenerative disease. All patients were in the chronic stage of the syndrome and abstinent from alcohol. Education level was assessed using seven categories based on level of education (in accordance with the Dutch educational system), 1 being the lowest (less than primary school) and 7 the highest (academic degree). The study was approved by the Ethics Committee of the Faculty of Social Sciences of Radboud University (Ref. no. ECSW2015-1210-343) and the institutional review boards of Korsakoff Center Atlant (Ref. no. mdz/mp/2015-005) and the Vincent van Gogh Institute for Psychiatry (CWOP; Ref. no. 15.04365). Written informed consent was obtained for all patients. If the patients were not legally competent, their legal representative also signed the informed consent form.

Table 1. Descriptive statistics of the sample

	***N* = 47**	**Range**
Age, *M (SD)*	61.5 (6.6)	38 – 70
Sex, % female	23.4	2 – 7
Education level, *median*	4.0	0.42 – 30.8
Abstinence in years, *M (SD)*	8.3 (6.5)	64 – 127
NART IQ, *M (SD)*	93.0 (19.0)	10 – 25
MoCA, *M (SD)*	17.7 (3.9)	
NPI-Q	***N* = 42**	
Number of symptoms, *M (SD)*	3.7 (2.5)	0 – 9
≥ 1 symptom, %	85.7	0 – 17
Total severity score, *M (SD)*	6.1 (4.8)	0 – 23
Total caregiver distress, *M (SD)*	6.0 (6.4)	

Note. MoCA = Montreal Cognitive Assessment; NART = National Adult Reading Test; IQ = estimate of premorbid verbal intelligence quotient; NPI-Q = Neuropsychiatric Inventory – Questionnaire.

Instruments

All participants completed six computerized executive function tasks. These tasks were adapted versions of the tasks Friedman et al. (2008) described and measured the executive components shifting (Category Switch and Number Switch Tasks), updating (Spatial 2-Back and Letter Memory Tasks) and inhibition (Stop Signal and Antisaccade Tasks). The tasks were programmed in PsychoPy version 1.83.03 and reaction times (in ms) were measured with a button-box. All tasks were subdivided into multiple blocks of trials, preceded by practice trials, and only correct trials were used to calculate outcome measures. Task instructions remained visible on the screen during each trial to avoid reduced performance due to memory deficits. The order of the tasks was counterbalanced. All tasks were extensively piloted and modified if necessary, confirming that administering to cognitively impaired individuals was feasible, yet avoiding ceiling performance in cognitively unimpaired individuals (see Moerman – van den Brink et al., 2019, for a more detailed description and Figure 1 for a schematic overview of the tasks).

Shifting

The Category Switch Task is designed to measure shifting ability by switching between two tasks: categorizing words into living/nonliving objects versus categorizing the same words into larger/smaller than a soccer ball. 150 ms before each trial, a cue (a picture of a heart for 'living/nonliving' and a soccer ball for 'larger/smaller than a soccer ball') indicated which instruction should be followed. The dependent variable was the switch cost, calculated as the difference between the median reaction time (RT) of the correct switch trials and the median RT of the correct no-switch trials.

The Number Letter Switch Task also contained switching between two tasks: to indicate whether a number-letter pair (e.g. 4 G, K3) was even/odd or to indicate the same number-letter pair as a vowel/consonant. The position of the number-letter pair (above or below a line) served as a cue for which task to be performed. Switch cost operated as the dependent variable.

Updating

The Spatial 2-Back Task was designed to measure updating ability. In this task, ten squares were placed in a circle. In each trial, one square was briefly highlighted for 500 ms, after which participants had to respond if this square was the same as the one highlighted two trials earlier. Participants were instructed to remember a series of two target locations, while constantly adding a new target location and ignoring the last target location. The dependent variable was the percentage of correct answers.

The Letter Memory Task also required constant updating of information. In this task, a letter was presented on the screen for 2,500 ms after which another letter was presented. After each letter, participants were required to verbally rehearse the last two letters presented. The dependent variable was the percentage of correct answers (as measured by the researcher).

Inhibition

The Antisaccade Task was designed to measure inhibition. In this task, participants were required to attend to the opposite direction of a briefly presented (150 ms) black square (22 x 22 mm), thus inhibiting the automatic tendency to make a saccade to that cue. After this cue, an open square with an arrow (16 mm) was presented at the opposite side for 175 ms, followed by a grey square masking the arrow. Participants were instructed to indicate whether the arrow was pointing to the left or to the right. We measured the percentage of correct answers as the dependent variable.

In the Stop Signal Task, participant first had to categorize a series of words as being an animal or non-animal as fast as possible. After 98 trials, they were instructed not to respond when they heard a tone (100 ms). This signal was presented in 25% of target trials at one of three possible times: 50 ms before the participant's average reaction time (calculated from the practice trials); 225 ms before the average reaction time or 50 ms after the onset of the trial. The dependent variable was the stop-signal RT, calculated following Friedman et al. (2008).

Neuropsychiatric symptoms

Neuropsychiatric symptoms were measured using the validated Dutch version of the Neuropsychiatric Inventory – Questionnaire (NPI-Q; Kaufer et al., 2000; De Jonghe et al., 2003). The NPI-Q is a brief informant version of the standard NPI and measures 12 domains of neuropsychiatric symptom. Caregiver/informants were first asked to indicate whether a symptom is present with "yes" or "no". In the case of "yes", informants rated the severity of that symptom on a 3-point Likert scale ("mild", "moderate" or "severe"). Total severity score is the sum of individual severity scores and can range from 0 – 36. The NPI-Q is widely used and has acceptable psychometric properties (Kaufer et al., 2000; Tate, 2010). Although informant reports have a potential bias, for instance ratings being affected by the quality of the relationship to the patient, the informant's perspective is likely to be more valid than the ratings from the patients with KS, as they typically lack insight into their own disorder, thus providing a less valid estimate of their neuropsychiatric symptoms (Arts et al., 2017; Gerridzen et al., 2019; Walvoort et al., 2016).

Other measures

Intelligence was estimated using the Dutch version of the National Adult Reading Test (NART; Schmand et al., 1992). General cognitive functioning was measured with the validated Dutch version of the Montreal Cognitive Assessment, version 7.1 (MoCA; Nasreddine et al., 2005).

Procedure

Patients were invited to participate if they fulfilled the inclusion criteria. Assessment sessions lasted up to 1.5 hours and were subdivided into blocks of 30 minutes, if necessary. The MoCA was completed prior to the assessment of the executive tasks. Professional caregivers (patients' primary nurses), who knew the patient well, completed the NPI-Q and provided other data such as demographics, medication use, abstinence period and medical history.

Analyses

Results were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Version 25. Details on the analyses of the executive tasks are described in Moerman – van den Brink et al. (2019). First, a factor analysis was conducted using principal axis factoring and direct oblimin rotation on the six experimental tasks to examine shared variance of the executive function tasks. Subsequently, factor scores were created using regression. Next, a regression analysis was performed to examine whether neuropsychiatric symptoms can be predicted by executive functioning, with the MoCA and the executive factor scores as predictors and

the NPI-Q total score as the dependent variable. In addition, two interaction effects were calculated to examine whether the MoCA moderates the relationship between the executive subcomponents and neuropsychiatric symptoms, by multiplying the z-scores of the MoCA and each factor score and adding this score as a predictor in the aforementioned regression analysis. We checked the assumptions of normality for all measures (by examining the P-P plots and the skewness and kurtosis statistics), and checked the specific assumptions for factor analysis and multiple regression analysis (e.g. linearity, homoscedastity, and the absence of multicollinearity).

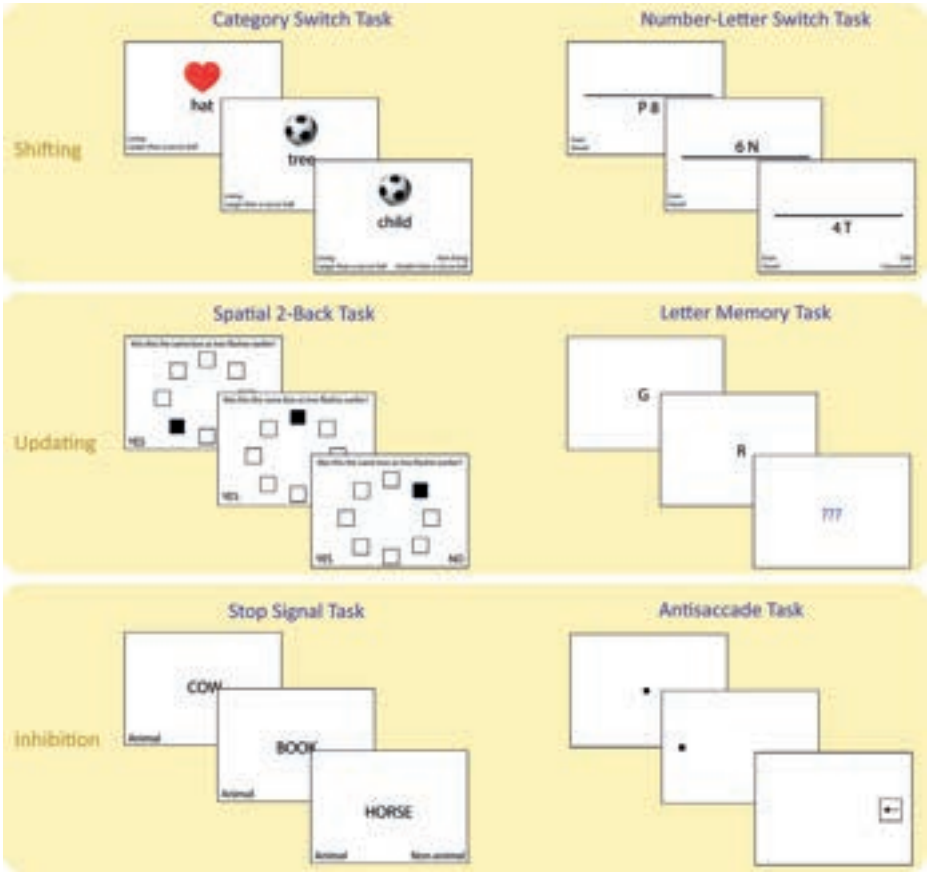

Figure 1. Schematic overview of the paradigms tapping into the three executive domains *shifting, updating* and *inhibition*

RESULTS

Table 1 shows the descriptive statistics of the NPI-Q. Most frequently reported symptoms included agitation/aggression (58.1%), irritability/lability (55.8%) and apathy (48.8%). Descriptive statistics for the executive functioning tasks are presented in Table 2. Table 3 shows three significant correlations, one between both shifting tasks, one between both updating tasks, and one between an updating (Spatial 2-Back task) and an inhibition task (Antisaccade task). The normality assumption was met and no violations of linearity, homoscedastity or multicollinearity were found.

A factor analysis was conducted on the executive function measures. The Kaiser-Meyer-Olkin measure was.55, which is acceptable. Based on eigenvalues >1 and the scree plot, a two-factor model was extracted. Table 4 shows the factor loadings after rotation. Factor 1 represents the shifting ability, while factor 2 is a combined representation of updating and inhibition. Table 5 shows the relationship between the executive function factors, the MoCA and the NPI-Q. Only the MoCA was significantly related to the NPI-Q. Also, a significant relationship was found between the MoCA and the Updating/inhibition factor. A regression analysis was executed with the NPI-Q as the criterion variable, with the MoCA and two executive factors as predictors. Additionally, to examine whether the MoCA serves as a moderator between the EF predictors and the NPI-Q, two interaction variables (MoCA x Shifting; MoCA x Updating/Inhibition) were added as predictors to the analysis. The model was not statistically significant ($F(5,39) = 1.62$; $p = .18$), see Table 6.

Table 2. Descriptive results of the executive function tasks

	N	*M*	*SD*	Min	Max	Skewness[a]	Kurtosis[a]
Shifting							
Category Switch, *ms*	45	1,265	1,215	-661	5464	1.39	2.83
Number Letter Switch, *ms*	46	1,611	1,131	-3	4037	0.86	-.20
Updating							
Spatial 2-Back, *% correct*	45	55.0	16.9	10.4	77.1	-1.34	1.22
Letter Memory, *% correct*	47	76.3	26.5	11.1	100	-.72	-.29
Inhibition							
Antisaccade, *% correct*	47	74.5	9.5	50.0	85.2	-.99	.31
Stop Signal, *ms*	45	540	146	297	963	.44	.19

[a]For accuracy measures, skewness and kurtosis are calculated from arcsine transformed scores.

Table 3. Intercorrelations (Pearson's *r)* between the z-scores of the executive function tasks (*N* = 45)

	Category Switch	Number Letter Switch	Letter Memory	Spatial 2-Back	Antisaccade
Number Letter Switch					
r	.49**				
N	45				
Letter Memory					
r	-.08	.26			
N	45	47			
Spatial 2-Back					
r	-.13	.17	.32*		
N	45	47	45		
Antisaccade					
r	.03	.28	.27	.50**	
N	45	47	47	45	
Stop Signal					
r	-.22	-.053	-.23	.27	.01
N	45	45	45	45	45

* *p* <.05; ** p <.001.

Table 4. Summary of factor analysis for the executive function measures

	Shifting	Updating/Inhibition
Category Switch task	**.798**	.108
Number Letter Switch task	**.702**	-.192
Letter Memory task	-.018	**.488**
Spatial 2-Back task	.088	**.734**
Antisaccade task	-.155	**.529**
Stop Signal task	-.246	-.290

Note. Factor loadings >.40 appear in bold. *N* = 44.

Table 5. Correlations (Pearson's *r*) between general cognitive functioning, executive functioning and neuropsychiatric symptoms in patients with Korsakoff's syndrome

	MoCA	Shifting	Updating/inhibition
Shifting			
r	.10		
N	44		
Updating/inhibition			
r	.38*	.03	
N	44	44	
NPI-Q			
r	-.43**	.03	-.01
N	43	40	40

Note. MoCA = Montreal Cognitive Assessment; NPI-Q = Neuropsychiatric Inventory – Questionnaire.
* $p < .05$ ** $p < .01$.

Table 6. Linear model of predictors of neuropsychiatric symptoms and their interaction effects

	B	*SE B*	β	*p*
Constant	6.18	.77		<.001
MoCA	-1.88	.79	-.39	.023
Shifting	.31	.92	.06	.740
Updating/inhibition	-.30	.94	-.06	.748
MoCA × Shifting	.83	.91	.15	.372
MoCA × Updating/inhibition	-.82	.82	-.16	.325

Note. $R^2 = .19$; $N = 40$; MoCA = Montreal Cognitive Assessment.

DISCUSSION

The aim of the present study was to examine the relationship between executive dysfunction and neuropsychiatric symptoms in patients with KS. With regards to the included executive functions, factor analysis resulted in a two-factor model with a combined factor of updating/inhibition, and a shifting factor. We did not observe any significant relations between these two executive factors on the one hand, and informant-based reports of neuropsychiatric symptoms on the other. General cognitive functioning was found to be related to neuropsychiatric symptoms. Finally, we did not find a moderating effect of the MoCA between executive dysfunction and neuropsychiatric symptoms.

In the current patient sample, neuropsychiatric symptoms were very common (85.7% of the patients with KS showed at least one symptom), this prevalence was

slightly lower than the 96.4% rate in a sample of KS patients reported by Gerridzen et al. (2018). For comparison, a systematic review of inpatients with dementia shows a mean prevalence rate of 82% of patients having at least one neuropsychiatric symptom (Selbaek et al., 2013). In addition to the brain dysfunction in KS, alcohol use disorder itself co-occurs with other psychiatric conditions (Hasin et al., 2007). These combined factors may explain the high prevalence of the neuropsychiatric symptoms found in KS samples, because some of these symptoms will also occur in the context of a psychiatric disorder.

With respect to executive functions, we found a two-factor model instead of a three- or nested-factor model previously described by Friedman and Miyake (2017). In accordance with earlier findings (Klauer et al., 2010), shifting could be dissociated from updating and working memory in the current study, with moderate inter-task correlations (.49) between the two shifting tasks and factor loadings >.70. This is in contrast to updating and inhibition, which could not be differentiated in the current patient sample. A two-factor model of executive function may reflect more unidimensionality within executive function organization in patients with KS than in healthy controls, which is in line with the idea that individuals with lower mental abilities show less differentiated cognitive profiles, also known as Spearman's law of diminishing returns (Spearman, 1927). Low test performances in people with lower mental abilities (due to younger age, lower intelligence or neurological disorders) might thus reflect a (diminished) general ability (g) rather than specific cognitive impairment. The unity/diversity model seems to capture the organization of executive functions mainly in cognitively healthy adult populations, which may not be applicable in lower-ability groups (Biesmans et al., 2019; Janssen et al., 2013; Karr et al., 2018). Earlier studies that found a significant association between executive dysfunction and neuropsychiatric symptoms (Brodaty et al., 2012; McPherson et al., 2002) did not take general cognitive functioning into account and used executive measures that could be argued to be task impure. The problem with the latter is that task-impure measures are likely influenced by other abilities such as processing speed, which are related to general cognitive functioning (Floyd et al., 2010; Salthouse, 2005). Studies that did control for general cognitive functioning found significant associations between general cognitive functioning and neuropsychiatric symptoms or apathy, but not for specific executive function measures (Brodaty et al., 2005; Senanarong et al., 2005). Current results suggest similar associations, since general cognitive functioning was correlated to neuropsychiatric symptoms, while the executive measures were not. Notwithstanding the results of the overall regression model, the correlation between general cognitive functioning and neuropsychiatric symptoms (r = -.43;

p <.01; see Table 5), and the magnitude of the standardized beta coefficient of general cognitive functioning (β = -.39; *p* =.023; see Table 6) confirms the association between general cognitive functioning and neuropsychiatric symptoms.

Some issues concerning task selection should be discussed. Executive dysfunction was measured with experimental tasks for which the psychometric properties (such as reliability and predictive validity) are unknown. However, the tasks used were adapted versions of Friedman et al. (2008), which are widely used to study executive dysfunction and to overcome task-impurity (Friedman, 2016; Snyder et al., 2015). Task adjustments for the current study resulted in a decrease in length and complexity, but did not, in our view, change the nature and validity of the tasks. Additionally, patients as well as cognitively unimpaired controls were able to complete the tasks without floor effects (Moerman – van den Brink et al., 2019). In addition, we did not use the tasks themselves as predictors in our model, but utilized their aggregated measures (established through factor analysis) in order to rule out non-executive task demands such as processing speed, or reading ability as much as possible. Another point of discussion concerns the measurement of neuropsychiatric symptoms. The NPI-Q was designed to measure neuropsychiatric symptoms from a broad spectrum (Tiel et al., 2015). It is possible that executive dysfunction is related to some neuropsychiatric symptoms (Gerridzen et al., 2018), but not to others. Moreover, the distinct neuropsychiatric symptoms are rated on a 3-point scale and are considered unidimensional, which might not be the case for all neuropsychiatric symptoms. Apathy, for instance, can be considered a multifaceted construct, with the presence of identifiable subtypes (Husain & Roiser, 2018; Radakovic & Abrahams, 2018C; Robert et al., 2010). Previous investigations aimed to identify clusters of neuropsychiatric symptoms on the NPI, such as 'hyperactivity', 'psychosis', 'affective syndrome' and 'apathy' (Aalten et al., 2008). We did not include clusters of the NPI-Q in our analyses due to the modest sample size. Sample size should also be taken into account when interpreting the non-significant results of the model, since general effects may have reached significance if a larger sample size was used. Given the modest sample size, we argue that our results are somewhat equivocal and should be treated with caution. However, while limited from an epidemiological perspective, our sample size of 47 patients with KS is still one of the largest KS samples to date in which detailed cognitive measurements have been performed (with study samples typically consisting of 15 to 25 cases; e.g. El Haj & Nandrino, 2018; Brion et al., 2017; Laniepce et al., 2019). Another point regarding our sample is that some clinical details are not available, such as the age at which KS was diagnosed or the average amount of alcohol consumed previously. However, such information is extremely difficult to validly obtain in patients with

KS as most patients are not able to reproduce this information correctly and in many cases there are no relatives who can give this sort of information. It is recommended that future studies, ideally in larger samples, should focus on more in-depth measures of neuropsychiatric and behavioral symptoms.

In sum, neuropsychiatric symptoms are highly prevalent in KS patients, in addition to profound executive deficits (Moerman – van den Brink et al., 2019). A two-factor model of executive function, with shifting and a combined factor of updating/inhibition, was not related to the presence and severity of neuropsychiatric symptoms. General cognitive functioning is found to be related to neuropsychiatric symptoms. Patients with severe cognitive deficits tend to have more neuropsychiatric symptoms. We argue that in patients with KS diminished cognitive differentiation may account for the absence of significant association between executive function and neuropsychiatric symptoms. The high prevalence of both cognitive and behavioral problems in KS motivates the need to investigate both constructs in more detail to develop better treatments or compensatory strategies for patients.

Chapter 5

The relation between Bbehavioral, emotional and cognitive apathy and everyday executive dysfunction in alcoholic Korsakoff's syndrome

Kessels, R. P. C., Moerman-van den Brink, W. G., Rensen, Y. C. M., van Aken, L., Walvoort, S. J. L., & Egger, J. I. M. (2021). The relation between behavioral, emotional and cognitive apathy and everyday executive dysfunction in alcoholic Korsakoff's syndrome. *Archives of Clinical Psychiatry, 48*(3), 178–181. https://doi.org/10.15761/0101-60830000000301

SUMMARY

Objective

Apathy is an important neuropsychiatric symptom in alcohol-related cognitive impairment in general, and Korsakoff 's syndrome in specific. However, research in patients with Korsakoff 's syndrome on the multifaceted nature of apathy is lacking. Aim of the current study was to examine behavioral, cognitive and emotional apathy in alcoholic Korsakoff patients, also investigating the association with overall cognitive and executive dysfunction.

Methods

We studied 43 patients with Korsakoff 's syndrome (mean age 60.9, SD=6.5, range 38-70) using the Apathy Evaluation Scale – Informant Version (AES-I) and also administered the Montreal Cognitive Assessment and the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) as a measure of daily executive problems.

Results

In our sample, 76% of the Korsakoff patients were classified as being apathetic. AES-I scores correlated with overall cognitive function and were related to observer-rated daily executive problems.

Conclusions

Apathy is highly prevalent in Korsakoff patients and related to overall cognitive dysfunction and everyday executive problems. Our results stress the need to further examine underlying mechanisms of apathy in Korsakoff patients and the need for interventions aimed at reducing apathy.

INTRODUCTION

Korsakoff's syndrome (KS) results from thiamine deficiency, mainly occurring following years of chronic alcohol use and malnutrition (Arts et al., 2017; Bowden, 1992). KS is characterized by chronic cognitive impairment, notably severe anterograde and retrograde amnesia, as well as executive dysfunction. Other symptoms include neuropsychiatric symptoms, such as apathy, confabulations, agitation/aggression, and disinhibition (Arts et al., 2017; Gerridzen et al., 2018), which are associated with higher caregiver burden and more frequent psychotropic drug use (Gerridzen et al., 2014).

Apathy as a neuropsychiatric symptom in KS was already discussed in early literature as avolition (Arts et al., 2017). It can be considered a disorder of motivation manifesting in the loss of goal-directed activity (Ang et al., 2017). Unfortunately, apathy has been poorly studied in patients with KS. An epidemiological study in 281 KS patients used the Neuropsychiatric Inventory – Questionnaire (NPI-Q), only containing one item about apathy ("Does the patient seem less interested in his/her usual activities or in the activities and plans of others"), rated by a professional caregiver showed a prevalence of 49.5% (Gerridzen et al., 2018). The Behavioral Rating Scale for Psychogeriatric Inpatients (GIP-28), also containing one item about apathy, was used as one of the outcome measure in a study in which KS patients were taught everyday activities, not showing a beneficial effect of that intervention on apathy symptom severity (Rensen et al., 2019). A recent KS study in 15 patients with and 15 without cerebrovascular disease investigated apathy using the Apathy Evaluation Scale (AES) and related apathy severity to related constructs (everyday activities, emotional bluntness, competency to consent, and executive dysfunction). However, that study did not find any correlations between apathy and these other constructs, possibly due to the small sample size (Oey et al., 2021).

There is increasing evidence that apathy is not a unitary construct, but consists of three core components: a cognitive, affective/emotional, and behavioral component (Ang et al., 2017; Marin et al., 1991), but the multidimensional nature of apathy has not been studied in KS using a validated apathy rating scale. Furthermore, with respect to the underlying mechanisms, apathy has been argued to be associated with executive dysfunction (McPherson et al., 2002; Meyer et al., 2015), which is also highly prevalent in KS (Arts et al., 2017). However, such an association has not been demonstrated in KS (Oey et al., 2021). It could be hypothesized that especially the cognitive and behavioral components of apathy correlate with everyday executive function in KS, but this relation has not yet been

studied. The current study aims to 1) investigate the three core components of the apathy syndrome in KS patients, and 2) relate them to overall cognitive dysfunction and everyday life executive dysfunction.

METHODS

Participants

Forty-three patients with KS participated in this study (see Table 1 for demographics). Of these, 34 were inpatients of Atlant Korsakoff centre of expertise in Beekbergen and 9 inpatients of the Centre of Excellence for Korsakoff and Alcohol-Related Cognitive Disorders of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. Patients participated in a larger study on cognitive and behavioral dysfunction in KS (Moerman – van den Brink et al., 2019), but the data reported in the present paper have not been published before. Inclusion criteria were: meeting the KS criteria,1 the DSM-5 criteria for Alcohol induced Major Neurocognitive Disorder, Amnestic-Confabulatory Type, no brain disorders unrelated to alcohol (e.g., stroke), and aged <70. All patients had to be in the chronic stage and abstinent from alcohol (M duration 6.6 years, range 5 months-16 years). All patients provided written informed consent; if patients were not legally competent, their legal representative also signed the informed consent form.

Materials

Apathy was measured with the Dutch version of the 18-item Apathy Evaluation Scale – Informant version (AES-I). Professional caregivers who knew the patient well rated the patients on a 4-point Likert scale (maximum score=72). A score of ≥42 indicates an apathy syndrome. Also, the cognitive (max=32), behavioral (max=20) and emotional (max=8) subscores were computed (Oey et al., 2021). General cognitive functioning was measured with the validated Dutch version of the Montreal Cognitive Assessment (MoCA; max=30, higher score reflects better cognitive function, score <25 indicative for substance-induced neurocognitive disorder (Buijnen et al., 2018). Observer-rated everyday executive functioning was assessed using the validated Dutch informant version of the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Roth et al., 2005) which includes the main subscales Metacognition and Behavioral Regulation, and 9 subscales (see Table 1), with higher scores reflecting more executive problems. Observer ratings were used rather than self-reports of daily executive problems, as impaired awareness of deficits is common in patients with alcohol-induced cognitive disorders.

Analyses

All analyses were performed in IBM SPSS 27.0. First, the normality of all variables was checked using Q-Q plots. Next, for descriptive purposes, we computed the number of patients who were rated at or above the established AES-I cut-off score indicative for an apathy syndrome, scored below the cut-off score on the MoCA and scored in the clinically impaired range on the BRIEF-A (i.e., >2 SD above the normative mean). Paired sample t-tests comparing the mean item scores per subscale were performed to enable direct comparisons between subscales with different ranges (α=0.05). Also we computed Pearson correlation coefficients (r) between the AES-I subscales, the BRIEF-A subscales and the MoCA (α=0.01).

RESULTS

The normality assumption was met for all variables. All patients performed below the cut-off score of 25 on the MoCA indicative for a substance-induced neurocognitive disorder. Thirty-one (72.1%) patients performed at or above the established AES-I cut off score indicative for an apathy syndrome. On the BRIEF-A 18 patients (41.9%) performed in the clinically impaired range. More severe cognitive (M=2.69, SD=0.74) than emotional (M=2.51, SD=0.83) apathy ratings were found (t(42)=2.08, P=0.044) and a trend towards more behavioral (M=2.69, SD=0.76) than emotional apathy (t(42)=1.8, P=0.081), but there were no differences between the cognitive and behavioral ratings (t(42)=0.1, P=0.907), see Table 1. Table 2 shows the correlations of the AES-I with the MoCA and the BRIEF-A. Significant correlations between the MoCA and AES-I Total score and AES-I Behavioral subscores ($r \geq |-.41|$) were found, but no significant correlations between the MoCA and AES-I Cognitive and AES-I Emotional ($r \leq |-0.36|$) subscores. None of the AES-I measures correlated significantly with the BRIEF-A Behavioral Regulation main scale or any of its subscales ($r \leq .38$). All AES-I subscales significantly correlated with the BRIEF-A Metacognition main scale and four of its subscales: Initiate, Working memory, Plan/Organize, and Task monitoring ($r \geq .43$), but not the subscale Organization of materials ($r \leq .36$).

Table 1. Demographic variables and results for the MoCA, AES-I and BRIEF-A main and sub-scales of the Korsakoff patients (*N*=43)

	Mean	***SD***	***Range***
Age	60.9	6.5	38–70
Sex (m:f) *N*	33:10		
MoCA	17.2	3.1	9–24
Education level *N*			
Low	24		
Average	12		
High	7		
AES-I			
Total score	48.4	12.7	25–70
Cognitive scale	21.5	5.9	10–32
Behavioural	31.5	3.8	5–20
Emotional	5.0	1.7	2–7
BRIEF-A			
Total Score	145.3	27.1	83–190
Behavioral Regulation Index	55.6	13.4	31–84
Inhibit	14.0	3.7	9–22
Shift	13.3	2.9	6–17
Emotional control	17.4	5.9	10–29
Self-monitoring	10.9	3.5	6-18
Metacognition Index	89.7	17.9	51–116
Initiate	18.1	3.7	10-24
Working memory	17.5	3.9	8–24
Plan/Organize	23.2	4.6	12–30
Task monitoring	13.0	3.5	6–18
Organization of materials	17.9	4.7	8–24

MoCA = Montreal Cognitive Assesment; AES-I = Apathy Evaluation Scale – Informant Version; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.

Table 2. Pearson correlation coefficients of the AES-I subscales with the BRIEF-A subscales and the Montreal Cognitive Assessment (MoCA)

	AES-I Scale			
BRIEF-A Scale	**Total**	**Cognitive**	**Behavioral**	**Emotional**
Behavioral Regulation Index	.27	.22	.25	.21
Inhibit	.38	.35	.34	.26
Shift	.27	.21	.28	.37
Emotional control	.10	.06	.10	.03
Self-monitoring	.23	.21	.20	.16
Metacognition Index	.60*	.56*	.57*	.50*
Initiate	.67*	.62*	.66*	.53*
Working memory	.52*	.48*	.50*	.46*
Plan/Organize	.51*	.46*	.50*	.43*
Task monitoring	.62*	.57*	.61*	.48*
Organization of materials	.36	.35	.28	.30
MoCA	-.41*	-.36	-.44*	-.20

* *P*<.01; AES-I = Apathy Evaluation Scale – Informant Version; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.

DISCUSSION

This study is the first to examine the multifaceted nature of apathy in KS. 72.1% of the KS patients could be classified as having an apathy syndrome, with highest ratings given on the cognitive and behavioral apathy subscales, compared to emotional apathy. With respect to executive problems in daily life as measured with the BRIEF-A, apathy was related to observed problems in metacognitive behavior, specifically with initiation, working memory, planning and organization. However, no correlations were found between any of the apathy subscales and the observed problems in behavioral regulations (shifting, inhibition, emotional control and monitoring). Our finding illustrates the need to further examine the relation between apathy and of observational and performance measures of executive function in KS.

Our study also has several limitations. First, although the prevalence of apathy in our sample was high, the range of some of the AES subscales is limited compared to the total score (with the emotional subscale only consisting of two items). Recently, the Apathy Motivation Index (AMI; Ang et al., 2017) was developed to overcome shortcoming of existing apathy scales that may not capture the full range of

apathetic symptoms, but this instrument has not been applied in KS yet. Another limitation is the modest sample size of 43 patients. Larger samples are needed to replicate and extend the current study (e.g., by performing factor analysis). Furthermore, apathy as a syndrome may overlap with depression (Oey et al., 2021), which we did not measure directly in the current study. Moreover, our measure of executive dysfunction was limited to an extensive behavioral assessment, but did not include performance-based measures of executive function. While it has been argued that behavioral assessment of executive function may be more ecological valid than the use of performance-based neuropsychological executive tests, performance-based tests may capture other aspects of executive function than behavioral ratings (Beerten-Duijkers et al., 2019). Studies in other disorders, for instance, have demonstrated correlations between apathy ratings and the performance on neuropsychological executive tests. That is, apathy was found to be related to tests of concept shifting, inhibition and working memory in Alzheimer's dementia (McPherson et al., 2002), and to response initiation, but not shifting or inhibition, in Parkinson's disease (Meyer et al., 2015). However, a study in frontotemporal dementia did not show any correlations between apathy and response initiation as a measure of executive function (Gonçalves et al., 2020). These mixed findings and the lack of studies on apathy in KS illustrate the need for more research on the cognitive correlates of apathy.

In all, we report a high prevalence of apathy in KS patients that involves the behavioral, cognitive and emotional apathy domains. Apathy severity was related to overall cognitive dysfunction. An association between apathy and metacognitive, but not behavioral, everyday executive problems was found. As apathy is associated with high caregiver burden and worse every-day functioning, interventions targeting apathy are clearly needed. Future studies using apathy measures with a more extensive scoring range and performance-based executive function measures in larger samples are required to further examine the underlying neurocognitive mechanisms of apathy in KS patients, which may result in a larger proportion of explained variance.

Chapter 6

Is executive dysfunction associated with apathy in patients with alcoholic Korsakoff's syndrome?

Moerman-van den Brink, W. G., Oey, M. J., van Aken, L., Oudman, E., Postma, A., Egger, J. I. M., & Kessels, R. P. C. (in preparation). *Is executive dysfunction associated with apathy in patients with alcoholic Korsakoff's syndrome?*

SUMMARY

Objective

This study aims to examine the relationship between executive dysfunction and apathy in patients with Korsakoff's syndrome (KS), taking the multifaced nature of both constructs into account.

Methods

Executive dysfunction was assessed in 86 KS patients (mean age 64.1; 24 woman) with the Digit Span subtask of the Wechsler Adult Intelligence Scale – Fourth edition to assess updating ability; the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test to assess shifting ability and the D-KEFS Color Word Interference Test to assess inhibition ability. Apathy was measured with the informant version of the Apathy Motivation Index (AMI), consisting of three subscales: Behavioral Activation, Social Motivation and Emotional Sensitivity. General cognitive functioning was measured with the Montreal Cognitive Assessment (MoCA). Hierarchical regression analyses were performed with the MoCA and depressive symptoms in step 1 and the three executive abilities in step 2 as predictors, and the AMI subtypes/ total score as dependent variables. Group differences between apathetic and non-apathetic KS patients were analyzed with an ANOVA.

Results

In KS patients, general cognitive dysfunction significantly predicted apathy variance in the AMI total score and in the AMI subtype Behavioral Activation. Among executive dysfunction, updating and shifting ability did not predict apathy or its subtypes in KS patients. Inhibition ability predicted variance in the AMI Social Motivation subtype. At the group level, apathetic patients had significantly lower general cognitive functioning. No significant differences in executive dysfunction were found.

Conclusions

In patients with KS, apathy is related to cognitive dysfunction, but not to executive dysfunction specifically.

INTRODUCTION

Korsakoff's syndrome (KS) is a neuropsychiatric disorder resulting from diencephalic brain damage due to thiamine deficiency after an incomplete recovery from a Wernicke encephalopathy. Patients with KS are characterized by severe and disproportionate episodic memory dysfunction in comparison to other cognitive impairments (Kopelman, 2022). In addition, neuropsychiatric symptoms, such as flattened affect, apathy, lack of illness insight and (possibly fantastic) confabulations may be present (Arts et al., 2017). In most patients, the thiamine deficiency occurs in the context of chronic or excessive alcohol abuse or alcohol use disorder. In alcoholic KS patients, executive dysfunction has been repeatedly demonstrated (Van Oort & Kessels, 2008; Maharasingam et al., 2013; Brion et al., 2014; Moerman-van den Brink et al., 2019). Even though it can be debated whether executive dysfunction should be considered part of KS itself or is due to the 'comorbid' alcoholic encephalopathy, these executive problems may hamper treatment outcomes in individuals with KS (Kopelman, 2022; Arts et al., 2017; Clergue-Duval et al., 2022).

Executive function (EF) refers to the ability to regulate one's thoughts, emotions and behavior and include higher-order, goal-directed cognitive processes such as planning, reasoning and problem-solving. Within EF, several cognitive processes can be distinguished. In Miyake's unity/diversity model, 'common EF' (previously referred to as an inhibition factor) on the one hand reflects the ability of goal-directed behavior (Friedman & Miyake, 2017). On the other hand, this model distinguishes two specific factors: shifting, that is, the ability to replace goals and corresponding behavior when necessary, and updating, the ability to replace information in working memory while preserving other relevant information. Earlier research on executive dysfunction in patients with KS has shown that shifting and updating are affected most, while inhibition or common EF seems to be relatively spared (Brion et al., 2017; Moerman-van den Brink et al., 2019; El Haj et al., 2022; Janssen et al., 2023).

As discussed above, neuropsychiatric symptoms, such as irritability, agitation, disinhibition and apathy, are common in patients with KS (Gerridzen et al., 2017; Gerridzen et al., 2019). However, the underlying mechanisms of these neuropsychiatric symptoms and their relationship with the cognitive deficits in patients with KS remain unclear and under debate. Research findings to date do not show strong, direct relationships between neuropsychiatric symptoms and EF problems in patients with KS. In an earlier study, we examined this relationship with tailored, component-specific executive tasks and assessed neuropsychiatric

symptoms with the Neuropsychiatric Inventory – Questionnaire (NPI-Q; Kaufer et al., 2000; de Jonghe et al., 2003). We found that the number of neuropsychiatric symptoms was related to the global level of cognitive dysfunction (i.e., the Montreal Cognitive Assessment, a screener of cognitive functioning), but not to executive dysfunction specifically (Moerman-van den Brink et al., 2020;).Furthermore, we reported a significant association between apathy and observer-rated, daily executive dysfunction (Kessels et al., 2021).

One of the most common neuropsychiatric symptoms in patients with KS is apathy, prevalent in around 50% of the patients with KS (Gerridzen et al., 2017; Moerman-van den Brink et al., 2020; van Dorst et al., 2021). Apathy is often defined as a disorder of motivation, resulting in a reduction of goal-directed activity in comparison to the person's previous level of functioning, which can be manifested in behavioral, cognitive and emotional or social aspects (Robert et al., 2018; Husain et al., 2018). Rather than being a unitary construct, apathy is now considered as a multidimensional syndrome with distinct subtypes, labeled as behavioral, emotional and social apathy (Robert et al., 2018; Ang et al., 2017). Apathy is commonly found in various brain disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease and is related to poor treatment outcomes (Vilalta-Franch et al., 2013; Robert et al., 2010; Muhammed et al., 2021; Krishnamoorthy & Craufurd, 2011; Starkstein et al., 2006). Individuals with more apathetic symptoms have lower levels of functional competence, and are less able to manage basis hygiene activities, as well as independent daily activities (Yeager & Hyer, 2008). Apathy is also positively related to high caregiver distress, poorer treatment outcome, increased cognitive decline, earlier need for long-term care, and a heightened mortality risk (Meiland et al., 2005; Dufournet et al., 2019; Zuidema et al., 2009; Mulders et al., 2016; Nijsten et al., 2017; Oey et al., 2021). In KS, both the patients themselves and their professional caregivers report high levels of apathy. Caregivers report slightly higher levels of apathy, possibly reflecting the diminished awareness of and insight into the deficits in patients with KS. Both patients and caregivers report social apathy as the most prominent symptom, compared to behavioral and emotional apathy (van Dorst et al., 2021) Although apathy is severely present in patients with KS, Oey and colleagues found that motivation to engage in pleasurable activities, as measured by the Pleasant Activity List, is unaffected. Therefore, there seems to be a contrast in which patients are motivated to engage in activities but do not act on them (Oey et al., 2021).

Several possible mechanisms underlying the clinical presentation of apathy have been postulated. These include cognitive mechanisms and reward-sensitive

processes in which several neurotransmitters (primarily dopamine) and various brain regions and networks are involved (Husain & Roiser, 2018; Tay et al., 2020; Dalléry et al., 2023).Motivated activity requires consecutive stages of action, in which EF plays a crucial role. For instance, mental flexibility is important for making a cost-benefit analysis, to settle on a choice, and to replace it, and is associated with working memory updating and shifting ability (Colautti et al., 2023). Common EF reflects the ability to maintain and manage goals which requires the inhibition of irrelevant stimuli and responses (Friedman & Miyaki, 2017; Dalléry et al., 2023). Both common EF and shifting ability seems to play a role in apathy, in performing an action as well as in performing different actions.

Research on the relationship between apathy and executive dysfunction in other clinical populations yielded mixed results. In Alzheimer patients, executive dysfunction (especially lack of initiative, measured with the Modified Six Elements Task) predicted levels of apathy (Esposito et al., 2010). A meta analytic review on this relationship in patients with Parkinson's Disease concluded that apathy scores (in the absence of depression or dementia) were related to inhibition dysfunction, but not shifting ability (D'Iorio et al., 2018). In patients with Huntington's disease, higher apathy scores were significantly associated with lower performance on a range of executive tasks, including fluency tasks, Trail Making Test Part B and the Stroop Color Word Test. However, when combined in a model, only motor symptoms and depression, but not EF, significantly predicted apathy scores (Hendel et al., 2023).

Building on our earlier research, this study further examines the relationship between EF and apathy in patients with KS. Given the multifaceted nature of both constructs, we will examine the key subcomponents of EF and apathy, namely shifting, updating and inhibition/common EF, and relate them to social, behavioral and emotional apathy. EF subcomponents will be measured with established neuropsychological tasks and apathy subtypes will be measured with the Apathy Motivation Index (Ang et al., 2017). We hypothesize that both shifting and inhibition problems, but not updating problems, are related to higher apathy scores. Previous research has shown that social apathy is affected most in KS patients, possibly making this subtype most strongly related to executive dysfunction (van Dorst et al., 2021).

METHODS

Participants

Eighty-six patients (24 woman) with KS participated in this study (mean age: 64.1; SD = 8.0; range 37 – 81). Forty-five of these were patients of Korsakoff Center of Expertise Atlant, a specialized long-term care facility for KS patients in Beekbergen, the Netherlands. Thirty-one of these were inpatients of KS Center of Expertise Slingedael, a specialized long-term care facility for KS patients in Rotterdam, the Netherlands, and ten were inpatients of the Centre of Excellence for Korsakoff and Alcohol-Related Cognitive Disorders of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. All patients met the DSM-5-TR (APA, 2022) criteria for Alcohol-induced major neurocognitive disorder, amnestic-confabulatory type (code: 291.1) and were abstinent from alcohol for at least 6 weeks. Education level was determined using seven categories based on the Dutch educational system, 1 being the lowest (less than primary school) and 7 the highest (academic degree).35 Mean education level was 4.3 (SD = 1.3; range 1 – 7). 26.4% of the patients had one or more DSM-classifications, including depression (9.2%), anxiety (1.1%), schizophrenia (3.4%), bipolar disorder (1.0%), posttraumatic stress disorder (4.6%) and other (9.2%). Psychotropic drugs were used by 54% of the study population. 33.3% used antipsychotics, 21.8% used antidepressants, 19.5% used benzodiazepines and 1.1% used mood stabilizers.

Instruments

Executive dysfunction was measured with three widely used and validated neuropsychological paper-and-pencil tasks. Updating ability was assessed with the Digit Span (DS) subtask of the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV; Wechsler, 2008). Updating ability was calculated as the total score of correct repeated series of digits of all three conditions, converted into a Wechsler standard score, based on age-adjusted norm data. Shifting ability was assessed with the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Delis et al., 2001). Shifting ability was calculated as the completion time of condition 4 (Letter-Number Switching) minus the mean completion time of conditions 2 and 3 (Number and Letter Sequencing respectively), converted into a standard score based on age-adjusted norm data. To assess inhibition, the D-KEFS Color Word Interference Test was used, which is based on the classic Stroop paradigm (Delis et al, 2001). Inhibition ability was calculated as the completion time for the third condition minus the average completion time for the first and second conditions, converted into a Wechsler standard score, based on age adjusted norm data. For all

executive tasks, a score of more than 1.5 standard deviations below the normative mean of each test was considered as impaired.

Procedure

The inclusion criteria were a valid KS diagnosis, and no other cognitive injury (such as a stroke) as documented in the medical charts. Patients who met the inclusion criteria were invited to participate. All patients signed informed consent forms and when they were not legally competent, their legal representative also signed the informed consent forms. The study was approved by the Ethics Committee of the Faculty of Social and Behavioural Sciences of Utrecht University (Ref: 20-400, 2020). Participants were invited to complete a neuropsychological battery at their residential care facility, in a quiet room and with a trained researcher. Prior to the executive measures participants completed the MoCA. The order of the executive tests was counterbalanced. After completing the neuropsychological assessment the GDS-15 was administered in an interview. Around the same time, the primary professional caregiver of the patients was asked to complete the observer-rated version of the AMI. Information on demographics, medication use and medical history was obtained from the patient's medical records. All data were stored in Castor EDC (2019).

Analyses

Results were analyzed using IBM Statistical Package for the Social Sciences (SPSS) Version 28 First, for descriptive purposes, the percentage of impaired patients was classified per test based on available normative data (i.e. more than 1.5 SD below the age-adjusted normative mean) or cut-off scores. Second, to analyze the relationship between executive dysfunction and apathy a hierarchical multiple regression analysis was performed with the total apathy score measured with AMI as dependent variable. General cognitive functioning and depressive symptoms were entered at stage one, the executive variables (shifting, updating and inhibition) were entered at stage two. Third, to analyze the relationship between executive dysfunction and the apathy subtypes, three multiple regression analyses were executed with general cognitive functioning and depressive symptoms as predictors at stage one and shifting, updating and inhibition as predictors at stage two. Each subtype of apathy served as a dependent variable. Fourth, to examine group differences between apathetic and non-apathetic patients an ANOVA was performed with neuropsychological measures and depression scores as dependent variables and group as an independent variable.

RESULTS

The data met the assumptions of linearity, multicollinearity and homoscedasticity. All variables except for the GDS-15 were normally distributed. From the total sample, 12 patients were excluded (see figure 1). Table 1 presents the descriptive statistics of the neuropsychological tests, the AMI, and the GDS-15, as well as the percentage of patients which scores could be classified as impaired based on the normative data of the tests.

A hierarchical, multiple regression analysis with the total AMI score as dependent variable was significant at step 1 with general cognitive functioning and depressive symptoms as predictors, but not in step 2 with the three executive measures as predictors. See Table 2 for the results. Of the individual predictors, only general cognitive functioning explained a significant proportion of variance in apathy scores, while depressive symptoms, updating, shifting and inhibition did not.

Additionally, three hierarchical multiple regression analyses were performed with general cognitive functioning and depressive symptoms as predictors in step 1 and the three executive measures as predictors at step 2. The three subtypes of apathy served as dependent variable. With behavioral activation as dependent variable, this resulted in a significant model at step 1, but not in step 2. None of the individual predictors explained a significant proportion of variance in behavioral activation apathy scores. For social motivation, the model was significant in step 1 and step 2. Of the individual predictors, only inhibition explained a significant proportion of variance in social motivation apathy scores. For emotional sensitivity, the model was significant in step 1, but not in step 2. Only general cognitive functioning explained a significant proportion of variance in social motivation apathy scores. See Table 2 for the statistics.

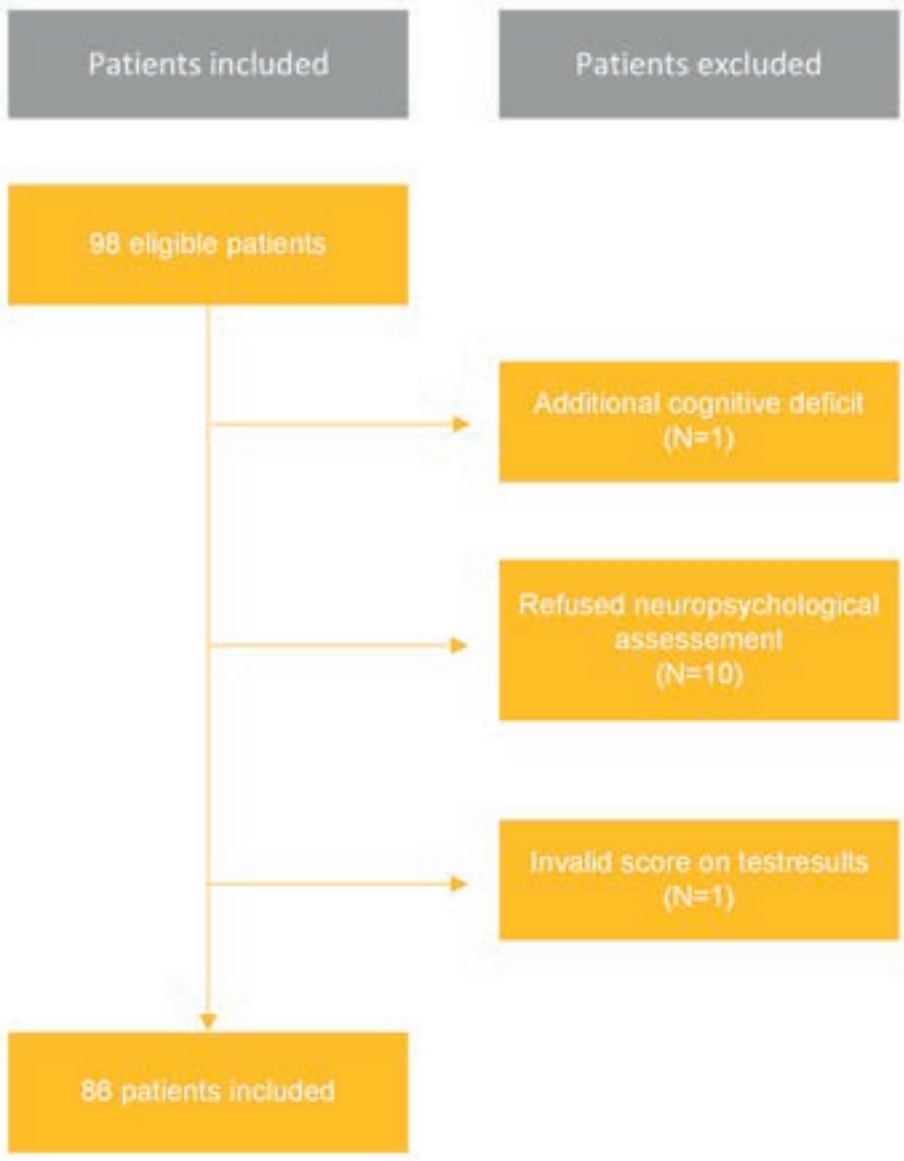

Figure 1. Flow chart of patient inclusion.

Table 1. Performance (raw mean scores, SD and range) on the neuropsychological tests, apathy and depression scores of patients with Korsakoff's syndrome

	N	Score Mean (SD); min-max; % impaired	% <1.5 SD below normative mean	Total number of errors[5] Mean (SD); min-max; % <1,5 SD below normative mean[2]
MoCA (max = 30)	86	18.6 (4.2); 6 – 28; 98.8		
DS (Updating)				
Forward (max = 16)	86	7.3 (1.9); 4 – 14		
Backward (max = 16)	86	6.4 (2.1); 2 – 13		
Sequencing (max = 16)	86	5.3 (3.1); 0 – 11		
Total (max = 48)	86	18.9 (6.3); 10 – 36		
Updating ability[1]	86		43	
D-KEFS TMT (Shifting)[4]				
Trail 1 Visual scanning	86	39.6 (17.1); 17 – 128	40.7	0.6 (1.2); 0 – 9;
Trail 2 Number sequencing	86	80.2 (35.7); 27 – 178	52.3	0.4 (1.0); 0 – 6;
Trail 3 Letter sequencing	86	93.2 (52.8); 23 – 230	51.2	1.1 (2.5); 0 – 11
Trail 4 Number-letter switching	84	183.2 (63.9); 56 – 345	60.7	7.3 (8.9); 0 – 32; 37.8%
Trail 5 Motor speed	86	64.9 (47.5); 17 – 251	27.9	0.5 (2.3); 0 – 16
Shifting ability[2]	84		13.1	
Inhibition (D-KEFS CWIT)[4]				
Card 1 Color naming	86	43.4 (11.1); 25 – 80	44.2	0.9 (1.4); 0 – 6
Card 2 Word reading	86	31.4 (9.2); 18 – 69	36.0	0.3 (0.8); 0 – 4
Card 3 Inhibition	82	90.3 (40.8); 44 – 276	32.9	3.8 (6.4); 0 – 35; 21.4%
Inhibition ability[3]	82		7.3	
AMI				
Total score (max = 4)	86	2.1 (0.7); 0.44 – 3.5; 75.6		
Behavioral activation (max = 4)	86	2.1 (0.9); 0.17 – 4.0; 72.1		
Social motivation (max = 4)	86	2.3 (0.9); 0.17 – 4.0; 74.4		
Emotional sensitivity (max = 4)	86	2.1 (0.8); 0.17 – 3.8; 69.8		
GDS-15 (max = 15)	86	2.0 (3)[6]; 0 – 13; 18.6		

Notes: [1]Updating ability was calculated as the total score of all three conditions, converted into a standard score, based on the age-adjusted norm data. [2]Shifting ability was calculated as the completion time of condition 4 (Letter-Number switching) minus the mean completion time of conditions 2 and 3 (Number and Letter Sequencing respectively), converted into a standard score based on age-adjusted norm data. [3]Inhibition ability was calculated as the completion time of Card 3 (Inhibition) minus the completion time of Card 1 and 2 (Color naming and Word reading), converted into a Wechsler standard score based on age-adjusted norm data.[4]Score is completion time in seconds. [5]Total errors for TMT trail 1 consist of omission and commission errors; for TMT trail 2, 3 and 4 of sequencing errors, set-loss errors and time discontinue errors; for TMT trail 5 of for TMT Trail 2, 3 and 4; total errors consist of discontinue errors for TMT Trail 5; Total errors consist of corrected and uncorrected errors for CWIT card 1, 2 and 3. Standard scores have a normative mean of 10 and an SD of 3. [6]Median and interquartile range is reported since data was not normally distributed.

Abbreviations: MoCA = Montreal Cognitive Assessment; DS = Digit Span; D-KEFS = Delis-Kaplan Executive Function System; TMT = Trail Making Test; CWIT = Color Word Interference Test; AMI = Apathy Motivation Index; GDS = Geriatric Depression Scale.

Table 2. Results of regression analyses with variables predicting apathy in patients with Korsakoff's syndrome (N = 80)

	Step 1 General cognitive functioning Depressive symptoms	**Step 2 Updating Shifting Inhibition**	**Individual predictor: General cognitive functioning**	**Individual predictor: Depressive symptoms**	**Individual predictor: Updating**	**Individual predictor: Shifting**	**Individual predictor: Inhibition**
AMI total score	**R^2 =.12; F(2, 77) = 5.2****	R^2 change =.06; F(3, 74) = 3.1	**β = -.312***	β =.134	β =.014	β =.139	β = -.205
AMI – Behavioral activation	**R^2 =.08; F(2, 77) = 3.2***	R^2 change =.009; F(3, 74) = 1.4	β = -.235	β =.157	β =.078	β =.047	β = -.076
AMI - Social motivation	**R^2 =.08; F(2, 77) = 3.7***	**R^2 change =.118; F(3, 74) = 3.8****	β = -.199	β =.087	β = -.171	β =.167	**β = -.233***
AMI - Emotional sensitivity	**R^2 =.08; F(2, 77) = 3.3***	R^2 change =.051; F(3, 74) = 2.2	**β = -.333***	β =.077	β =.131	β =.131	β = -.197

Note: *$p < 0.05$; **$p < 0.01$

Abbreviations: AMI = Apathy motivation index.

Figure 2 shows the results on overall cognitive functioning, depressive symptoms and the 240 three executive functions for individuals with apathy (mean AMI score > 1.66) and those without 241 apathy. ANOVA revealed that there was a statistically significant difference in general cognitive 242 functioning scores between apathetic and nonapathetic patients with KS ($F(1,84) = 8.2$; $p = .005$), 243 with apathetic KS patients have lower MoCA scores ($M = 17.9$; $SD = 4.2$) than nonapathetic 244 patients with KS ($M = 20.9$; $SD = 3.7$). No significant between-group differences were found on 245 any of the executive measures. There was also no significant difference in depressive symptom 246 scores between apathetic and nonapathetic patients with KS.

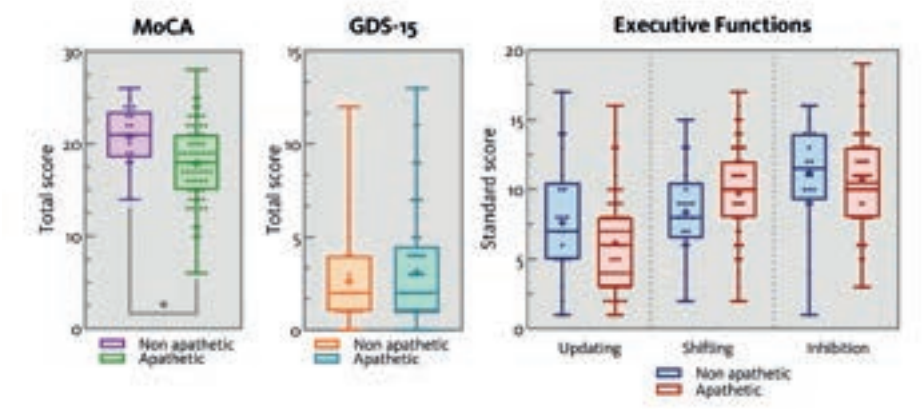

Figure 2. Box and whisker plots showing the results for general cognitive functioning (MoCA total score), depressive symptoms (GDS-15 total score) and the executive functions updating (WAIS-IV Digit Span standard score), shifting (D-KEFS Trail Making Test shifting contrast standard score) and inhibition (D-KEFS Color-Word Interference Test interference contrast standard score). The boxes indicate the 25th and 75th percentile, the center line represents the median, the + represents the mean, and the whiskers the minimum and maximum values. * $p < 0.05$

DISCUSSION

This study aimed to examine the relationship between EF and apathy in patients with KS. Overall, apathy was highly prevalent; with three-quarters of patients labeled as apathetic. Executive dysfunction prevalence was mixed, with updating ability being most affected, while inhibition ability had the lowest prevalence. Furthermore, our study identified a significant correlation between general cognitive functioning, as measured by the MoCA, and the presence of apathy in patients with KS, revealing compromised performance in both domains. We did

only find minimal associations between EF and apathy. Variance in apathy scores was mainly predicted by general cognitive functioning. That is, adding executive functions to the model did not result in more explained variance for the apathy subtypes, except for social motivation, which was additionally explained by inhibition ability.

Although adequate goal management (which requires both shifting and updating ability) was one of the most postulated possible mechanisms underlying apathy, an association between these constructs was not found in the current study. One notable psychometric result of this study should be taken into account; for shifting and inhibition, the ability score was measured as the contrast of reaction time scores between several conditions, thus accounting for individual differences in speed (Lezak et al., 2012). However, we found that up to 61% of patients with KS were more than 1.5 SD slower than the age-adjusted normative mean and up to 38% made more mistakes compared to the normative mean. It can be debated whether updating or shifting ability can be accurately measured when speed and accuracy requirements are not fully met. Part of the task demands is that they are performed under time pressure. In general, EF performances rely on underlying cognitive primitives such as motor speed, processing speed and visual perception. If patients are impaired at this level, higher-order cognitive tasks (including those measuring EF) may be less accurate indicators of EF ability (Biesmans et al., 2019). Furthermore, the association with general cognitive functioning may be due to the phenomenon that people with lower mental ability, due to younger age or lower intelligence have a less differentiated cognitive profile (Spearman, 1927; Biesmans et al., 2019; Moerman-van den Brink et al., 2020). The MoCA score used in current research reflects general cognitive ability, and therefore probably explains apathy primarily, whereas executive dysfunction did not explain significant additional variance in the hierarchical model.

Another perspective on EF and motivation is to distinguish executive function into 'hot' and 'cold' EFs. Cold EFs are core cognitive functions that are evaluated in emotionally neutral contexts, such as in the present study. Hot EFs, on the other hand, are involved in situations that rely on emotional and motivational processing, and are for example measured with gambling tasks (Brand et al., 2005). It is possible that the lack of a relationship between EF and apathy can be explained by the fact that only cold EFs were measured in current study. To date, limited research has examined the performance of individuals with KS on tasks measuring hot EF, revealing that patients with KS performed significantly lower on a gambling task than healthy controls and patients with KS are also found to

be impaired at emotional recognition (Brand et al., 2005; Montagne et al., 2006). Further investigation is needed to clarify EF performances of patients with KS on hot EF-tasks and the relationship between EF and apathy scores.

The current study has several strengths. The sample size is relatively high, since most studies on KS that measure in-depth cognitive or behavioral processes typically include smaller samples (~20-30 individuals). Further, our patient group was carefully selected with a clear and valid diagnosis of KS and no other comorbid brain diseases. Our sample as a whole reported few depressive symptoms, which is relevant since some symptoms of depression overlap with those of apathy notably diminished interest in activities, but not depressed mood (APA, 2022). The study assessed executive dysfunction with widely used, established and validated clinical tasks, which have also been previously applied in research on KS patients (Pollux et al., 1995; Welch et al., 1997; El Haj & Moustafa, 2023).

Our study also has some limitations. First, apathy is measured with an observational rating scale completed by the primary professional caregiver. However, this bears the risk that apathy was underreported, as the caregiver may have compared the participant's observations with those of other inpatients rather than with the general population. Further research could include other methods to quantify apathy, such as structured observations of specific behavior. Second, the tests applied in the current study only have age-adjusted normative data. To overcome this, future studies could include a control group of cognitively unimpaired adults. To compare the mechanisms of apathy across clinical conditions, future studies could also include non-Korsakoff psychiatric or neurological samples.

The present findings also contribute to the ongoing debate about the core clinical features of patients with KS (Arts et al., 2017; Janssen et al., 2023; Kopelman, 2023; Scalzo & Bowden, 2023; Wijnia, 2022). While there are to date no widely accepted clinical criteria for diagnosing KS, all definitions include severe memory dysfunction as the core feature of the syndrome (Victor et al., 1971; Kopelman et al., 2009) . Part of the current debate focuses on whether the definition of KS should be expanded to include non-memory cognitive deficits, such as executive dysfunction. Our results indicate that only a small proportion of patients performed more than 1.5 standard deviations below the normative mean on widely used clinical executive tasks. The current research group, however, is dependent on 24-hour care and many of them have been assigned a legal representative who is responsible for making decisions on their behalf and managing their finances, and thus can be considered severely cognitively affected. Earlier research

showed that when executive dysfunction is measured on a behavioral level with the BRIEF-A, only 41.9% of the patients could be classified as clinically impaired (Kessels et al., 2021). This shows that executive dysfunction is not the only factor underlying the often severe functional disability in everyday life in these patients. Our findings underscore the clinical heterogeneity within the KS population according to executive dysfunction. EF deficits may be related to alcoholic encephalopathy for instance volume loss in the prefrontal cortex and thus should be considered the result of co-morbidity in alcoholic KS patients rather than a necessary symptom in the thiamine-induced syndrome itself (Janssen et al., 2023; Pitel et al., 2012; Brion et al., 2014). Additionally, earlier research found that patients with KS who suffered from an infection during the Wernicke Encephalopathy (which precedes KS) have lower EF-performance during follow-up than patients without infections (Wijnia et al., 2016).

In summary, apathy is highly prevalent in patients with KS, but it is not associated with the level of executive dysfunction. Patients with higher levels of apathy tend to have lower general cognitive functioning. Moreover, while executive dysfunction is prevalent in patients with alcoholic KS, it is not present in all patients. Future research should clarify which factors are associated with EF dysfunction in patients with alcoholic and non-alcoholic KS. Given its high prevalence, the construct of apathy needs to be investigated in more detail, which will help to develop better treatments or compensatory strategies for patients with KS.

Chapter 7

Summary and discussion

This thesis aimed to better understand the profile and occurrence of executive function (EF) impairments in patients with Korsakoff's syndrome (KS) and to examine their relation with neuropsychiatric symptoms. In this chapter, an overview of the main findings will be provided, followed by a discussion of theoretical and clinical considerations. In addition, the strengths and limitations of the studies in this thesis will be discussed and clinical recommendations will be made.

SUMMARY

Clinical practice and empirical findings indicate that both behavioral and neuropsychiatric symptoms are common in patients with KS. **Chapter 2** presents a comprehensive review of the existing evidence regarding the prevalence and severity of these symptoms in patients with KS. A total of fifteen studies were included in the review. The studies exhibited considerable heterogeneity in terms of their methodological quality, measurement instruments, and classification criteria. The highest prevalence rates were observed for depressive symptoms and disorders, agitation/aggression, and psychotic symptoms and disorders. The severity scores indicated high rates of apathy. There were notable differences in prevalence and severity scores, and no studies were primarily designed to estimate the prevalence or severity of behavioral symptoms in patients with KS.

Chapter 3 examined the profile of executive dysfunction in patients with KS. In this investigation, the unity/diversity model proposed by Friedman and Miyake (2017) was utilized, incorporating three key factors: shifting, updating, and inhibition. To investigate the Miyake et al factors for this particular population, six tailor-made, computerized tasks designed to measure the three factors as process-pure as possible were used. The performance of 36 patients with KS was compared with those of 30 matched healthy controls. Compared to the control group, patients showed the lowest performance on tasks measuring shifting, followed by updating. On tasks measuring inhibition, patients' performance did not differ significantly from those of the control group. Patients performed above the chance level on all tasks, indicating that the tasks were appropriate for this cognitively impaired target group.

In **Chapter 4**, the relationship between executive dysfunction and neuropsychiatric symptoms was explored in 47 patients with KS. The study revealed that over 85% of patients with KS exhibited at least one neuropsychiatric symptom. The main research question was whether specific executive subcomponents could predict the variance in neuropsychiatric symptoms. First, a factor analysis was conducted on the scores

from the aforementioned six tasks, which supposedly assess the three EF factors shifting, updating, and inhibition. From this, a two-factor model was extracted, consisting of a shifting-specific factor and a combined updating/inhibition factor. The regression analysis revealed that none of the executive factors were found to predict the variance in neuropsychiatric symptoms. A significant relationship was identified between general cognitive functioning (as measured by the Montreal Cognitive Assessment, the MoCA) and neuropsychiatric symptoms. The more severe the cognitive impairments, the more neuropsychiatric symptoms are present in patients with KS.

In **Chapter 5**, the construct of everyday EF was operationalized through the administration of an observer-rated questionnaire, the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A). The questionnaire assesses EF in everyday life and includes two indexes: the Behavioral Regulation Index and the Metacognition Index. The study in this chapter aimed to investigate the association between daily EF and apathy. Apathy was assessed using the informant version of the Apathy Evaluation Scale (AES-I), with particular attention paid to the identification of distinct subtypes, that is, behavioral, cognitive, and emotional apathy. In this sample of 43 patients with KS, 72.1% of patients with KS were classified as apathetic with the highest ratings given on the cognitive and behavioral apathy subscales, compared to emotional apathy. Furthermore, apathy severity was found to be related to metacognitive everyday EF, but not to behavioral EF. Finally, apathy severity was found to be related to overall cognitive dysfunction, as measured by the MoCA.

The objective of the study in **Chapter 6** was to further examine the relationship between executive dysfunction and apathy, now taking into account the multifaceted nature of both constructs. EF was studied using established paper-and-pencil tasks. In this study, the three executive factors shifting, updating, and inhibition were each represented by a single neuropsychological task. Apathy was assessed using the informant version of the Apathy Motivation Index (AMI). This questionnaire includes three subscales measuring apathy: Behavioral Activation, Social Motivation, and Emotional Sensitivity. In a sample of 86 KS patients, over 75% of the patients could be classified as apathetic. There was no significant difference in executive functioning between the group of patients with KS classified as apathetic and the non-apathetic patients with KS. However, the apathetic group had significantly worse general cognitive functioning as measured by the MoCA. General cognitive functioning predicted the variance in apathy scores, while executive tasks performance did not. Looking at specific executive subdomains, inhibition ability appeared to predict the variance in social motivation apathy.

GENERAL DISCUSSION

Executive dysfunction in patients with KS

The term "executive function" is used to describe the capacity to regulate one's own behavior, emotions, and cognitions in order to maintain control over one's life (Goldstein & Naglieri, 2014). This capacity has been associated with both professional achievement and quality of life (Diamond, 2013). As discussed in the general introduction, there is considerable debate in the scientific literature regarding the operationalization of this construct, and a variety of models have been proposed. The present thesis employs the unity/diversity model proposed by Miyake and Friedman (2017) to examine EF, not with the primary goal to test the validity of the model itself, but to use the factors described by Friedman and Miyake to evaluate EF in patients with KS.

In this thesis, three different methods were employed to assess EF: (1) theory-driven, tailored measures designed to maximize process purity; (2) classic pen-and-paper neuropsychological tasks commonly used in clinical practice to investigate cognitive impairment; and (3) behavioral questionnaires. This multimethod approach encompasses both functional and activity-based perspectives on EF (conform the ICF-model, World Health Organization, 2001). This prompts the question of whether the different levels of measurement assess the same underlying concept. As mentioned in the general introduction of this thesis, neuropsychological tasks measuring EF differ in their ecological validity (i.e., the degree to which the test reflects and predicts real-world behavioral phenomena) and task purity (i.e., the degree to which the outcomes of the test are affected by non-executive processes such as language and processing speed). The behavioral questionnaires appear to be the most closely aligned with performance in everyday life, while the computerized tasks are designed to measure EF as process-pure as possible. The various measurement methods employed in this thesis therefore have distinct purposes, advantages, and disadvantages (Kessels, 2019). The central aim of this thesis was to examine the severity, occurrence, and profile of executive dysfunction in patients with KS and its relationship with neuropsychological symptoms. In the following sections, the results obtained for each function are set forth, and tentative conclusions are offered about the executive dysfunction in patients with KS.

Profile of executive dysfunction

The results of the study in Chapter 3 indicate that there is no evidence to support the existence of a three-factor structure in patients with KS. Instead, the results of the studies in this thesis suggest that the EF organization in people with KS is more

uniform than diverse, that is, a two-factor model of EF was found in the sample of patients with KS. One of the identified factors was a shifting factor but updating and inhibition could not be differentiated in the current patient sample, resulting in a combined factor of updating and inhibition. A considerable number of studies have reported difficulties in replicating Miyake's model, and the limited replicability of the model is one of its key criticisms (Silva, Carthery-Goulart & Lukasova, 2024). In particular, an executive model comprising solely two factors is more frequently observed in older adults, as shown in a review and reanalysis by Karr et al. (2018), suggesting that executive abilities de-differentiate with advancing age. It is also possible that EF undergoes de-differentiation in the presence of global cognitive impairment. As this thesis also examined the three factors independently, the subsequent discussion will address shifting, updating, and inhibition separately.

Shifting

The findings of this thesis indicate that patients with KS show significant deficits in their shifting ability. Shifting ability requires the capacity to substitute goals or task sets, subsequently acting in accordance with the substituted goal of task set (Friedman & Miyake, 2017). This EF factor appears to be the most severely affected in comparison to the other EF. This finding was observed both in Chapter 3, where computerized tasks were employed, and Chapter 6, where classic paper-and-pencil tasks were utilized. As detailed in Chapter 3, patients with KS showed a markedly inferior performance on both shifting tasks compared to the control group, with a substantial effect size. In Chapter 6, the patients' performances were compared with an age-adjusted reference group. Results showed that over 60% of patients with KS had impaired shifting ability. This percentage is higher than the observed impairments in both updating (43%) and inhibition (32%). Patients required more time and made more errors on tests designed to assess this ability. Shifting ability was also found to be compromised at a behavioral level, as reported by caregivers in the BRIEF-A Flexibility subscale. Caregiver ratings of patients with KS fell within the clinically impaired range. The underlying items of this scale pertain, for instance, to difficulties in transitioning from one activity to another, the challenge in accepting that solutions to problems may vary, the capacity to adapt to change, and the tendency to become distressed when unexpected changes occur in one's daily routine.

"I am quite rigid when I have to get out of bed. Then they really have to pull me out of bed with three men. I do have a little trouble with it. I feel like you have to do things here against your will." – Woman with KS, 56 years old

"A lot of people really appreciate having a daily schedule. I'm sure I'm one of them. You wouldn't make them happy if you suddenly changed it." – Man with KS, 67 years old

Updating

It appears that the updating ability of people with KS is affected to varying degrees when measured by neuropsychological tasks. In Chapter 3, KS patients performed significantly worse than controls on tasks measuring updating function, with a large effect size. Effect sizes differed between nonverbal and verbal updating, the latter being most impaired. Chapter 6 showed that, compared to age-adjusted normative data, 43% of patients performed more than 1.5 SD below the normative mean on the Digit Span (DS) subtest of the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV). According to Friedman and Miyake (2017), updating requires the constant replacement of information in working memory and is thus closely related to the construct of working memory, which also involves the manipulation of information. Moreover, updating is often operationalized with tasks assessing working memory. It has previously been demonstrated that working memory is impaired in patients with KS (van Geldorp et al., 2011; Arts et al., 2017; Pitel et al., 2009; Eikelboom et al., 2024; Oudman et al., 2019). The results of this thesis corroborate these findings and provide evidence on the frequency and severity of working memory problems in patients with KS. On a behavioral level, updating ability was measured with the Working Memory subscale of the BRIEF-A, the mean ratings on this subscale were classified as clinically significant. The mean score on the BRIEF-A Working Memory subscale refers to patients' challenges with concentration, task completion, maintaining focus in conversation, short-term memory and multitasking.

"I'm having a hard time getting on top of things. I really need an agenda. I like that. I want to know where I stand." – Man with KS, 67 years old

Inhibition

The results of the study in Chapter 3 suggest that inhibition ability is minimally impacted by KS. Inhibition ability was measured using a verbal and a non-verbal computerized task. These tasks required patients to categorize stimuli, with categorization rules changing during the task, forcing the patient to switch appropriately. In both tasks, patients performed above chance level, and their mean performance was not significantly different from that of the control group.

However, patients demonstrated a significant decrease in the speed of their categorization process and exhibited a significantly higher error rate compared to the control group. In Chapter 6 inhibition ability was assessed with the Color Word Interference Test (CWIT) of the Delis-Kaplan Executive Function System. Compared with age-adjusted normative data, about one-third of the patients performed more than 1.5 SD below the normative mean on the Inhibition condition, indicative of an impaired performance. Notably, only 7.3% of the patients demonstrated scores more than 1.5 SD below the normative mean when the contrast score was calculated. At the behavioral level, the mean score on the Inhibition subscale of the BRIEF-A was not clinically significant. This subscale identifies behaviors such as having difficulty waiting or sitting still, making inappropriate sexual comments, being easily distracted or acting impulsively. The results of this thesis indicate that problems with inhibition are not a prominent feature of KS. This contrasts with earlier research who reported inhibition problems in patients with KS using computerized assessment (Janssen et al., 2023; El Haj et al., 2020). The divergent outcomes may be attributable to variations in the tasks employed and the type of outcome measure utilized to assess inhibition. Contrary to the conclusion that inhibition problems may not be a prominent feature of KS, many behaviors are observed in clinical practice that may be indicative of inhibition problems. These include aggression and agitation, sexually inappropriate behavior, disinhibited eating, smoking, and excessive consumption of coffee or soda. It is possible that these types of behavioral problems are not common, but when only a few patients on a unit exhibit these behaviors, it is still a tremendous burden on caregivers and requires a great deal of attention from the multidisciplinary treatment team.

"I got a robot cat, and I like to play with it. Now I've been having trouble stopping. Sometimes I can't even stop at night. Now that I've taken the battery out, someone else is going to stop me, and I don't like that. – Woman with KS, 56 years old

"I'll just keep eating."– Man with KS, 77 years old

Executive dysfunction and cognitive primitives

In the neuropsychological tasks employed in Chapters 3 and 6 for both shifting and inhibition ability, reaction times served as the outcome measure, which were then used to compute a contrast score. This contrast score denotes the difference in reaction times between comparable task conditions with and without an

executive (i.e., shifting, inhibition) component (cf. Donders, 1868/1969). In other words, the utilization of a contrast score facilitates the differentiation between the executive aspects of a given task and the underlying cognitive processes, including processing speed and language ability. Patients diagnosed with KS were slower on all task conditions, even in the baseline conditions, compared to healthy controls (Chapter 3) or to age-adjusted normative data (Chapter 6). In Chapter 6, a higher percentage of patients performing more than 1.5 SD below the normative mean is identified when using reaction time alone compared to the contrast score (60.7% versus 13.1% for shifting ability and 32.9% versus 7.3% for inhibition ability). This confirms that using contrast scores, individual differences in cognitive primitives such as speed are minimally reflected in the results of executive tasks. Nonetheless, the efficacy of this approach in cases of severe problems with these cognitive primitives is debatable. It is plausible that individuals with below-average speed may require less additional time to shift or inhibit, resulting in a smaller contrast score. This could create the impression of optimal EF, despite the fact that the score is predominantly influenced by the cognitive primitives rather than actual 'higher-order' executive functioning (see also Biesmans et al., 2018).

Executive dysfunction in context

A multimethod approach is used in this thesis to examine the extent of executive dysfunction in patients with KS, including neuropsychological testing and behavioral questionnaires. A significant proportion of individuals with KS did not perform in the abnormal range at the test level, a finding that is consistent with clinical practice where, in many instances, executive test results for individuals with KS do not indicate abnormalities. However, a range of issues have been observed in clinical practice that may be associated with executive dysfunction, including lack of initiative, and difficulty in monitoring and organizing daily activities. Furthermore, the patients with KS who participated in this study were residing in institutionalized settings and were dependent on 24-hour care. The majority of them had designated either a formal or informal representative to make decisions on their behalf (Gerridzen & Goossensen, 2014), a fact that in itself can be indicative for EF problems. It is important to note that detecting EF problems in patients with KS is challenging, and the context of the assessment can influence the results obtained. The extent of EF problems observed in neuropsychological testing is affected by the choice of test and the outcome measure used, as discussed above. The context also impacts the reporting of EF problems at the behavioral level. In a structured environment characterized by high levels of care, EF problems may be less noticeable than in an environment where EF skills are highly demanded.

Consequently, the precise role of context emerges as a potential area for further investigation in the study of EF problems in patients with KS.

Executive dysfunction and neuropsychiatric symptoms (notably apathy)

As outlined above, EF is an important domain to assess in patients with KS, in particular because it is assumed to be associated with behavioral or neuropsychiatric symptoms. Neuropsychiatric symptoms are common in individuals with KS. For example, among patients residing in long-term care facilities, 96.4% have at least 1 neuropsychiatric symptom, and nearly half (45.8%) have 5 or more symptoms (Gerridzen et al., 2018). The presence of neuropsychiatric symptoms contributes to caregiver burden in this population. One of the most prominent neuropsychiatric symptoms in patients with KS is apathy. In the present thesis, three-quarters of patients were classified as apathetic (see Chapters 4, 5, and 6). Apathy is characterized as a disorder of motivation, manifesting as a decline in goal-directed activity relative to an individual's previous level of functioning. The conceptualization of apathy encompasses a multifaceted syndrome (Kos et al., 2016), comprising distinct subtypes such as behavioral, emotional, and social apathy (Robert et al., 2018; Ang et al., 2017). Apathy can be measured by self-report or clinician administered questionnaires, such as the Apathy Evaluation Scale (AES). The AES was used in this thesis, but has also been criticized for assessing apathy as a unitary construct. Consequently, a recently developed questionnaire was also employed in this thesis, the Apathy Motivation Index (AMI). The AMI is a multidimensional instrument that aims to identify subtypes of apathy, including behavioral, social and emotional apathy.

One of the central inquiries of this thesis concerns the relationship between neuropsychiatric symptoms, with a particular focus on apathy, and executive dysfunction in patients diagnosed with KS. A significant correlation was identified between the Apathy Evaluation Scale (AES) and the BRIEF-A Metacognition scale. However, no substantial relationship was observed between the Neuropsychiatric Inventory - Questionnaire (NPI-Q) and computerized EF tasks. Additionally, no significant relationship was observed between the Apathy Motivation Index (AMI) and three paper-and-pencil EF tasks. However, a significant correlation was identified between the AES, the NPI-Q, and the AMI with general cognitive functioning, as measured by the Montreal Cognitive Assessment (MoCA). The findings suggest that more severe general cognitive functioning impairment is associated with a higher prevalence of neuropsychiatric symptoms and apathy.

Previous research has examined the link between neuropsychiatric symptoms and EF problems in various neurodegenerative disorders. A review of studies on cognitive correlates of neuropsychiatric symptoms in patients with Parkinson's disease found links between executive dysfunction and neuropsychiatric symptoms including apathy (Alzahrani & Venneri, 2015). A recent review and meta-analysis found a link between neuropsychiatric symptoms and worse global cognition and executive dysfunction in people with different types of dementia (Sabates et al., 2023). However, many of the studies included in both reviews did not find a relationship between EF and neuropsychiatric symptoms. One explanation is that when this relationship is examined in patient groups, the relative variability of both EF problems and neuropsychiatric symptoms is small, making it difficult to detect underlying relationships. However, a relationship between neuropsychiatric symptoms and global cognition was identified in this thesis. The presence of neuropsychiatric symptoms is likely determined by a multitude of factors, including biological, psychological, social, and cognitive elements (Sabates et al., 2023). The aforementioned studies have predominantly aimed to isolate cognitive factors, the present thesis similarly focuses exclusively on assessing the cognitive correlates of neuropsychiatric symptoms. The relative influence of other factors also determines the strength of the relationship found between EF and neuropsychiatric symptoms.

In conclusion, the manifestation of neuropsychiatric symptoms and the severity of apathy in patients with KS are influenced by the extent of cognitive dysfunction. Specifically, the more severe the cognitive impairment, the more pronounced the neuropsychiatric symptoms and apathy.

CLINICAL AND RESEARCH RECOMMANDATIONS

Patients with KS are a heterogeneous group with varying degrees of cognitive impairment, somatic disorders and psychiatric comorbidity. These patients frequently hesitate to seek medical care and typically possess a limited social support network, which often complicates the process of obtaining a precise diagnosis due to the absence of crucial (informant-verified) information. Also, for many patients residing in long-term care facilities, the initial diagnosis of KS was established years prior to inclusion in this study, which further complicates the reliability of the diagnosis. In the selection of the participants for this thesis, the objective was to exclude patients with additional brain disorders, such as a brain tumor, traumatic brain injury or neurodegenerative pathology (e.g., cerebrovascular pathology or Alzheimer’s disease). However, due to the aforementioned challenges,

it cannot be discounted that some patients with comorbid neuropathology may have been included. Additionally, no consensus on diagnostic criteria for KS exist to date (Arts et al., 2017). This challenges the diagnostic process in clinical practice, but also contributes to the heterogeneity of the study group. It is therefore recommended that international consensus be reached on the utilization of neuropsychological testing in the diagnostic process and the establishment of well-defined diagnostic criteria.

KS is a condition necessitating highly specialized care and treatment, with a low incidence in the general population (see also Palm et al., 2022). Within the Dutch healthcare system, KS is one of the patient populations that have been designated by the Dutch Ministry of Health as "Low Volume, High Complexity" (LVHC). This low prevalence is reflected in the typical sample sizes of studies on KS, which often consists of 10-20 participants. Such small samples increase the probability of chance findings unrelated to the core KS caused by outliers due to co-morbidity or other confounding factors (i.e. a Type I error). Moreover, small samples also result in low statistical power, increasing the probability of a type II error. The care structure established in the LHVC patients with a national knowledge network (the Korsakoff Knowledge Center; www.korsakovkenniscentrum.nl) facilitates cooperation between the specialist institutions in both mental-health care and long-term care. Therefore, as demonstrated in this thesis, the inclusion of a larger cohort of patients is estimated to be feasible. Furthermore, EF impairments have been observed in other LVHC patient populations, such as those with Huntington's disease or Traumatic Brain Injury. Subsequent research can concentrate on comparing the EF impairments among the aforementioned patient groups to investigate whether there are specific executive dysfunction profiles in the various disorders.

The use of executive tasks in neuropsychological assessment of patients with severe impairments is challenging. In addition to the aforementioned issues with task purity and ecological validity, findings from this thesis show that many individuals with KS exhibit limited processing speed, which may result in task conditions not being met. This is particularly relevant for tasks where reaction speed is a component of final score, as previously discussed. Therefore, it is recommended that these limitations be taken into account when interpreting the test results. The incorporation of observational questionnaires in neuropsychological assessment is recommended but also has inherent constraints. As patients are typically institutionalized during neuropsychological examinations, the questionnaire may assess behaviors that are not pertinent to the patient's daily activities. To illustrate, the majority of institutionalized patients are not required to engage in

the preparation of meals and are encouraged to adhere to the established schedule of their daily activities. As a result, it is challenging to ascertain whether patients possess these abilities. Furthermore, there is a possibility of observational bias. Typically, the completion of behavioral observation lists is undertaken by caregivers, who may be inclined to make comparisons between the performance of different patients rather than making comparisons with healthy controls. This may result in an insufficient frame of reference and a potential overestimation of the patient's abilities. It is recommended that the assessment of EF disorders not be limited to neuropsychological test results but also incorporate other measurement levels such as behavioral questionnaires, in addition to observation and interview data.

LIVING WITH EXECUTIVE DYSFUNCTION

A significant proportion of patients diagnosed with KS reside in long-term care facilities. As part of this thesis, a group of patients residing in Korsakoff Center of Expertise Markenhof, Atlant, were interviewed to discuss their experiences with EF problems. Many patients with KS have limited insight into their illness, which affects their perception of EF problems. In this interview, however, it was observed that some patients were able to recognize at least some of the problems discussed, either in themselves or in their peers. An important question in clinical practice pertains to the identification of suitable treatment for EF disorders. As one patient articulated, *"It's a very important topic, because it's so fundamental. I also learned that it's not that you can't learn it anymore. When you talk about Korsakoff's syndrome, you are talking about 20 shades of gray."* The demand for training or treatment also originates from nurses and other healthcare practitioners. In recent decades, specific methodologies have been developed for KS, including errorless learning and the empathic directive approach. One of the most significant challenges faced by caregivers of individuals with KS relates to the management of behavioral problems. While these behavioral problems are associated with cognitive impairments, it appears that the presence and severity of neuropsychiatric symptoms cannot be predicted solely from EF problems. Furthermore, the physical and social environment plays a crucial role in influencing the emergence and intensity of behavioral problems. The concept of behavior is more extensive and encompasses more than just neuropsychiatric symptoms. There is currently no specific treatment available for EF disorders in KS. Due to the persistence of the underlying brain damage, treatments are instead oriented towards restoring functionality and enhancing independence and quality of life. Individuals diagnosed with KS require specialized attention for their EF impairments in daily care. It is recommended that the physical and social

environments are designed to minimize demands on aspects of flexibility, the ability to inhibit behavior, and working memory. Overall, people with KS tend to benefit from a structured daily routine, consistent schedules, and a predictable environment. Additionally, behavioral management strategies should be employed to address problematic behaviors, encourage patient participation in activities, and foster healthy routines (van Dorst et al, 2024). One patient said, *"Research on this should really pay off. What can be done for the people with Korsakoff's syndrome? Do you need to assist somewhere? Can you help them? And we should not to wait for that."*

The quotations presented in this chapter have been included with the informed consent of the patients in question.

References
Research data management
Nederlandse samenvatting
Dankwoord
Curriculum Vitae
List of publications

REFERENCES

A

Aalten, P., van Valen, E., de Vugt, M. E., Lousberg, R., Jolles, J., & Verhey, F. R. (2006). Awareness and behavioral problems in dementia patients: A prospective study. *International Psychogeriatrics, 18*(1), 3–17. https://doi.org/10.1017/S1041610205002772

Aalten, P., Verhey, F. R. J., Boziki, M., Brugnolo, A., Bullock, R., Byrne, E. J., Camus, V., Caputo, M., Collins, D., De Deyn, P. P., Elina, K., Frisoni, G., Holmes, C., Hurt, C., Marriott, A., Mecocci, P., Nobili, F., Ousset, P. J., Reynish, E., … Robert, P. H. (2008). Consistency of neuropsychiatric syndromes across dementias: Results from the European Alzheimer Disease Consortium. *Dementia and Geriatric Cognitive Disorders, 25*(1), 1–8. https://doi.org/10.1159/000111082

Alderdice, F. A., McGuinness, C., & Brown, K. (1994). Identification of subtypes of problem drinkers based on neuropsychological performance. *The British Journal of Clinical Psychology, 33*(4), 483–498. https://doi.org/10.1111/j.2044-8260.1994.tb01145.x

Alzahrani, H., & Venneri, A. (2015). Cognitive and neuroanatomical correlates of neuropsychiatric symptoms in Parkinson's disease: A systematic review. *Journal of the Neurological Sciences, 356*(1–2), 32–44. https://doi.org/10.1016/j.jns.2015.06.037

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). American Psychiatric Association.

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders: DSM-5-TR* (5th ed., text revision). American Psychiatric Association Publishing.

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence, 8*(2), 71–82. https://doi.org/10.1076/chin.8.2.71.8724

Ang, Y. S., Lockwood, P., Apps, M. A. J., Muhammed, K., Husain, M., & Gulinello, M. (2017). Distinct subtypes of apathy revealed by the Apathy Motivation Index. *PLOS ONE, 12*(1), e0169938. https://doi.org/10.1371/journal.pone.0169938

Arts, N. J., Walvoort, S. J., & Kessels, R. P. (2017). Korsakoff's syndrome: A critical review. *Neuropsychiatric Disease and Treatment, 13*, 2875–2890. https://doi.org/10.2147/NDT.S130078

B

Baggetta, P., & Alexander, P. A. (2016). Conceptualization and operationalization of executive function. *Mind, Brain, and Education, 10*(1), 10–33. https://doi.org/10.1111/mbe.12100

Bento, M. A., Vieira, J. B., Silva, M. L., & Camolas, J. (2023). Case report: Wernicke-Korsakoff syndrome after bariatric surgery. *Frontiers in Nutrition, 10*, 1321275. https://doi.org/10.3389/fnut.2023.1321275

Bertens, D., Fasotti, L., & Kessels, R. P. C. (2023). Ecological validity of neuropsychological assessment. In G. J. Boyle, Y. Stern, D. J. Stein, B. J. Sahakian, C. J. Golden, T. M. Lee, & S. A. Chen (Eds.), *The SAGE Handbook of Clinical Neuropsychology* (pp. 23–38). SAGE Publications Ltd. https://doi.org/10.4135/9781529789539

Biesmans, K. E., Aken, L., Frunt, E. M. J., Wingbermühle, P. A. M., & Egger, J. I. M. (2019). Inhibition, shifting, and updating in relation to psychometric intelligence across ability groups in the psychiatric population. *Journal of Intellectual Disability Research, 63*(2), 149–160. https://doi.org/10.1111/jir.12559

Blansjaar, B. A., Horjus, M. C., & Nijhuis, H. G. (1987). Prevalence of the Korsakoff syndrome in The Hague, The Netherlands. *Acta Psychiatrica Scandinavica, 75*(6), 604–607.

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 Psychiatrica Scandinavica, 86*(3), 240–246.

Bouma, A., Mulder, J., Lindeboom, J., & Schmand, B. (Eds.). (2012). *Handboek neuropsychologische diagnostiek* (2nd ed.). Pearson Assessment and Information B.V.

Bowden S. C. (1992). Is there more than one neuropsychological disorder commonly associated with alcohol dependence? *Drug and Alcohol Review*, *11*(3), 299–304. https://doi.org/10.1080/09595239200185831

Bowden, S., Bardenhagen, F., Ambrose, M., & Whelan, G. (1994). Alcohol, thiamin deficiency, and neuropsychological disorders. *Alcohol and Alcoholism. Supplement*, *2*, 267–272.

Boyle, M. H. (1998). Guidelines for evaluating prevalence studies. *Evidenced-Based Mental Health*, *1*(2), 37–39. https://doi.org/10.1136/ebmh.1.2.37

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*(3), 267–277. https://doi.org/10.1037/0894-4105.19.3.267

Brion, M., D'Hondt, F., Lannoy, S., Pitel, A., Davidoff, D. A., & Maurage, P. (2017). Crossmodal processing of emotions in alcohol-dependence and Korsakoff syndrome. *Cognitive Neuropsychiatry, 22*(5), 436–451. https://doi.org/10.1080/13546805.2017.1373639

Brion, M., D'Hondt, F., Pitel, A. L., Lecomte, B., Ferauge, M., de Timary, P., & Maurage, P. (2017). Executive functions in alcohol-dependence: A theoretically grounded and integrative exploration. *Drug and Alcohol Dependence*, *177*, 39–47. https://doi.org/10.1016/j.drugalcdep.2017.03.018

Brion, M., Dormal, V., Lannoy, S., Mertens, S., de Timary, P., & Maurage, P. (2018). Imbalance between cognitive systems in alcohol-dependence and Korsakoff syndrome: An exploration using the Alcohol Flanker Task. *Journal of Clinical and Experimental Neuropsychology*, *40*(8), 820–831. https://doi.org/10.1080/13803395.2018.1438371

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. https://doi.org/10.3389/fnhum.2014.00498

Brodaty, H., Connors, M. H., Xu, J., Woodward, M., Ames, D., & PRIME study group (2015). The course of neuropsychiatric symptoms in dementia: a 3-year longitudinal study. *Journal of the American Medical Directors Association*, *16*(5), 380–387. https://doi.org/10.1016/j.jamda.2014.12.018

Brodaty, H., Heffernan, M., Draper, B., Reppermund, S., Kochan, N. A., Slavin, M. J., Trollor, J. N., & Sachdev, P. S. (2012). Neuropsychiatric symptoms in older people with and without cognitive impairment. *Journal of Alzheimer's Disease, 31*(2), 411–420. https://doi.org/10.3233/JAD-2012-120169

Brodaty, H., Sachdev, P., Withall, A., Altendorf, A., Valenzuela, M., & Lorentz, L. (2005). Frequency and clinical, neuropsychological, and neuroimaging correlates of apathy following stroke: The Sydney Stroke Study. *Psychological Medicine, 35*(12), 1707–1716. https://doi.org/10.1017/S0033291705006173

Brokate, B., Hildebrandt, H., Eling, P., Fichtner, H., Runge, K., & Timm, C. (2003). Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: Continuity or discontinuity? *Neuropsychology, 17*(3), 420–428. https://doi.org/10.1037/0894-4105.17.3.420

Bruijnen, C. J. W. H., Jansen, M., Dijkstra, B. A. G., Walvoort, S. J. W., Lugtmeijer, S., Markus, W., De Jong, C. A. J., & Kessels, R. P. C. (2018). The Montreal Cognitive Assessment as a cognitive screen in addiction health care: A validation study for clinical practice. *Journal of Substance Use, 24*, 47–54. https://doi.org/10.1080/14659891.2018.1497102

Bruijnen, C. J. W. H., Walvoort, S. J. W., Dijkstra, B. A. G., de Jong, C. A. J., & Kessels, R. P. C. (2021). The Course of Cognitive Performance during Inpatient Treatment in Patients with Alcohol Use Disorder with No, Mild or Major Neurocognitive Disorders. *Alcohol and Alcoholism, 56*(1), 89–100. https://doi.org/10.1093/alcalc/agaa100

Butters, N., & Cermack, L. S. (1980). Alcoholic Korsakoff's syndrome: An information-processing approach to amnesia. Academic Press.

C

Caine, D., Halliday, G. M., Kril, J. J., & Harper, C. G. (1997). Operational criteria for the classification of chronic alcoholics: Identification of Wernicke's encephalopathy. *Journal of Neurology, Neurosurgery, and Psychiatry, 62*(1), 51–60.

Chen, C. T., Chang, C.-C., Chang, W.-N., Tsai, N.-W., Huang, C.-C., Chang, Y.-T., Wang, H.-C., Kung, C.-T., Su, Y.-J., Lin, W.-C., Cheng, B.-C., Su, C.-M., Hsiao, S.-Y., Hsu, C.-W., & Lu, C.-H. (2017). Neuropsychiatric symptoms in Alzheimer's disease: Associations with caregiver burden and treatment outcome. *QJM: An International Journal of Medicine, 110*(9), 565–570. https://doi.org/10.1093/qjmed/hcx077

Chen, S., Sultzer, D., Hinkin, C., Mahler, M., & Cummings, J. (1998). Executive dysfunction in Alzheimer's disease: Association with neuropsychiatric symptoms and functional impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences, 10*(4), 426–432. https://doi.org/10.1176/jnp.10.4.426

Cheon, Y., Park, J., Joe, K. H., & Kim, D. J. (2008). The effect of 12-week open-label memantine treatment on cognitive function improvement in patients with alcohol-related dementia. *The International Journal of Neuropsychopharmacology*, *11*(7), 971–983. https://doi.org/10.1017/S1461145708008663

Clergue-Duval, V., Barré, T., Cognat, E., et al. (2022). Patients with severe alcohol-related cognitive impairment improve in flexibility when abstinence is maintained: A comparative study with Alzheimer's disease. *Frontiers in Psychology, 13*, 936639. https://doi.org/10.3389/fpsyg.2022.936639

Colautti, L., Iannello, P., Silveri, M. C., & Antonietti, A. (2023). Decision-making under ambiguity and risk and executive functions in Parkinson's disease patients: A scoping review of the studies investigating the Iowa Gambling Task and the Game of Dice. *Cognition and Emotion, 23*(5), 1225–1243. https://doi.org/10.3758/s13415-023-01106-3

Cummings, J. L., Mega, M., Gray, K., et al. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology, 44*(12), 2308–2314. https://doi.org/10.1212/WNL.44.12.2308

D

Dalléry, R., Saleh, Y., Manohar, S., & Husain, M. (2023). Persistence of effort in apathy. *Revue Neurologique (Paris), 179*(10), 1047–1060. https://doi.org/10.1016/j.neurol.2023.03.017

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System (D–KEFS) [Database record]. APA PsycTests. https://doi.org/10.1037/t15082-000

Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

D'Iorio, A., Maggi, G., Vitale, C., Trojano, L., & Santangelo, G. (2018). "Pure apathy" and cognitive dysfunctions in Parkinson's disease: A meta-analytic study. *Neuroscience & Biobehavioral Reviews, 94*, 1–10. https://doi.org/10.1016/j.neubiorev.2018.08.004

Donders F. C. (1868/1969). On the speed of mental processes. *Acta Psychologica*, *30*, 412–431. https://doi.org/10.1016/0001-6918(69)90065-1

Draper, B., Karmel, R., Gibson, D., Peut, A., & Anderson, P. (2011). Alcohol-related cognitive impairment in New South Wales hospital patients aged 50 years and over. *The Australian and New Zealand Journal of Psychiatry*, *45*(11), 985–992. https://doi.org/10.3109/00048674.2011.610297

Drost, R., Postma, A., & Oudman, E. (2019). Cognitive and affective theory of mind in Korsakoff's syndrome. *Acta Neuropsychiatrica, 31*(3), 128–134. https://doi.org/10.1017/neu.2018.35

Dufournet, M., Dauphinot, V., Moutet, C., Verdurand, M., Delphin-Combe, F., & Krolak-Salmon, P. (2019). Impact of cognitive, functional, behavioral disorders, and caregiver burden on the risk of nursing home placement. *Journal of the American Medical Directors Association, 20*(10), 1254–1262. https://doi.org/10.1016/j.jamda.2019.03.027

E

Egger, J. I. M., Wester, A. J., De Mey, H. R. A., & Derksen, J. J. L. (2002). Korsakoff's syndrome on the MMPI-2. *Acta Neuropsychiatrica, 14*(5), 231–236. https://doi.org/10.1034/j.1601-5215.2002.140506.x

Eikelboom, W. S., Goette, W. F., Rensen, Y. C. M., van Nuland, J. C., Janssen, G. T. L., & Kessels, R. P. C. (2024). Measuring episodic verbal learning ability in alcohol-related cognitive disorders in relation to everyday functioning. *Addiction Neuroscience, 11*. https://doi.org/10.1016/j.addicn.2024.100144

El Haj, M. (2021). Autobiographical memory in Korsakoff syndrome: A review. *L'Encephale, 47*(4), 356–361. https://doi.org/10.1016/j.encep.2020.11.013

El Haj, M., & Moustafa, A. A. (2023). "Ten dollars today or 50 dollars after one month?" Temporal discounting in Korsakoff syndrome. *Cognitive Neuropsychiatry, 28*(2), 116–129. https://doi.org/10.1080/13546805.2023.2173059

El Haj, M., & Nandrino, J. L. (2017). Phenomenological characteristics of autobiographical memory in Korsakoff's syndrome. *Consciousness and Cognition*, *55*, 188–196. https://doi.org/10.1016/j.concog.2017.08.011

El Haj, M., & Nandrino, J. L. (2018). Seeing life through rose-colored spectacles: Autobiographical memory as experienced in Korsakoff's syndrome. *Consciousness and Cognition, 60*, 9–16. https://doi.org/10.1016/j.concog.2018.02.007

El Haj, M., Moustafa, A. A., & Robin, F. (2022). "Remember to take your medication": Prospective memory in Korsakoff's syndrome. *Journal of Clinical and Experimental Neuropsychology, 44*(4), 272–280. https://doi.org/10.1080/13803395.2022.2110574

El Haj, M., Nandrino, J. L., Coello, Y., Miller, R., & Antoine, P. (2017). Source monitoring in Korsakoff's syndrome: "Did I touch the toothbrush or did I imagine doing so?". *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *91*, 262–270. https://doi.org/10.1016/j.cortex.2017.02.006

Esposito, F., Rochat, L., Van der Linden, A. C., et al. (2010). Apathy and executive dysfunction in Alzheimer disease. *Alzheimer Disease and Associated Disorders, 24*(2), 131–137. https://doi.org/10.1097/WAD.0b013e3181c9c168

F

Ferran, J., Wilson, K., Doran, M., et al. (1996). The early onset dementias: A study of clinical characteristics and service use. *International Journal of Geriatric Psychiatry, 11*(9), 863–869. https://doi.org/10.1002/(SICI)1099-1166(199610)11:10<863::AID-GPS394>3.0.CO;2-7

Fisk, J. E., & Sharp, C. A. (2004). Age-related impairment in executive functioning: Updating, inhibition, shifting, and access. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 874–890. https://doi.org/10.1080/13803390490510680

Floyd, R., Bergeron, R., Hamilton, G., & Parra, G. (2010). How do executive functions fit with the Cattell-Horn-Carroll model? Some evidence from a joint factor analysis of the Delis-Kaplan executive function system and the Woodcock-Johnson III tests of cognitive abilities. *Psychology in the Schools, 47*, 721–738. https://doi.org/10.1002/pits.20500

Fournier-Vicente, S., Larigauderie, P., & Gaonac'h, D. (2008). More dissociations and interactions within central executive functioning: A comprehensive latent-variable analysis. *Acta Psychologica, 129*(1), 32–48. https://doi.org/10.1016/j.actpsy.2008.04.004

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: A latent-variable analysis. *Journal of Experimental Psychology: General, 133*(1), 101–135. https://doi.org/10.1037/0096-3445.133.1.101

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *86*, 186–204. https://doi.org/10.1016/j.cortex.2016.04.023

Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General, 137*(2), 201–225. https://doi.org/10.1037/0096-3445.137.2.201

G

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 wards in a general psychiatric hospital. *Tijdschrift voor Alcohol- en Drugsgebruik en andere Psychotrope Stoffen, 20*(1), 20–31 [in Dutch].

Gaugler, J. E., Yu, F., Krichbaum, K., & Wyman, J. F. (2009). Predictors of nursing home admission for persons with dementia. *Medical Care*, *47*(2), 191–198. https://doi.org/10.1097/MLR.0b013e31818457ce

Gerridzen, I. J., & Goossensen, M. A. (2014). Patients with Korsakoff syndrome in nursing homes: Characteristics, comorbidity, and use of psychotropic drugs. *International Psychogeriatrics, 26*(1), 115–121. https://doi.org/10.1017/S1041610213001543

Gerridzen, I. J., Joling, K. J., Depla, M. F., Veenhuizen, R. B., Verschuur, E. M. L., Twisk, J. W. R., & Hertogh, C. M. P. M. (2019). Awareness and its relationships with neuropsychiatric symptoms in people with Korsakoff syndrome or other alcohol-related cognitive disorders living in specialized nursing homes. *International Journal of Geriatric Psychiatry*, *34*(6), 836–845. https://doi.org/10.1002/gps.5093

Gerridzen, I. J., Joling, K. J., Depla, M. F., Veenhuizen, R. B., Verschuur, E. M. L., Twisk, J., & Hertogh, C. M. (2019). Awareness and its relationships with neuropsychiatric symptoms in people with Korsakoff syndrome or other alcohol-related cognitive disorders living in specialized nursing homes. *International Journal of Geriatric Psychiatry, 34*(6), 836–845. https://doi.org/10.1002/gps.5093

Gerridzen, I. J., Moerman-van den Brink, W. G., Depla, M. F., Verschuur, E. M. L., Veenhuizen, R. B., Wouden, J. C., Hertogh, C. M., & Joling, K. J. (2017). Prevalence and severity of behavioral symptoms in patients with Korsakoff syndrome and other alcohol-related cognitive disorders: A systematic review. *International Journal of Geriatric Psychiatry, 32*(3), 256–273. https://doi.org/10.1002/gps.4636

Gleichgerrcht, E., Chade, A., Torralva, T., Roca, M., & Manes, F. (2011). Comparing the neuropsychiatric profile of patients with Alzheimer disease who present spared versus impaired executive functioning. *Current Gerontology and Geriatrics Research, 2011*, 1–5. https://doi.org/10.1155/2011/514059

Goldstein, S., & Naglieri, J. A. (Eds.). (2013). *Handbook of executive functioning*. Springer.

Gonçalves, S. A. B., Caramelli, P., Mariano, L. I., Guimarães, H. C., Gambogi, L. B., Resende, E. P. F., Teixeira, A. L., & de Souza, L. C. (2020). Apathy in frontotemporal dementia is related to medial prefrontal atrophy and is independent of executive dysfunction. *Brain Research, 1737*, 146799. https://doi.org/10.1016/j.brainres.2020.146799

H

Haalboom, R., van Aken, L., Walvoort, S. J. W., Egger, J. I. M., & Kessels, R. P. C. (2019). Preserved intellectual functioning in Korsakoff's syndrome? Actual and premorbid intelligence in patients with major or mild alcohol-related cognitive disorder. *Journal of Substance Use, 24*(5), 532–538. https://doi.org/10.1080/14659891.2019.1619101

Harding, A., Halliday, G., Caine, D., & Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain, 123*(1), 141–154. https://doi.org/10.1093/brain/123.1.141

Hasin, D., Stinson, F., Ogburn, E., & Grant, B. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 64*(7), 830–842. https://doi.org/10.1001/archpsyc.64.7.830

Hatoum, A. S., Rhee, S. H., Corley, R. P., Hewitt, J. K., & Friedman, N. P. (2018). Do executive functions explain the covariance between internalizing and externalizing behaviors? *Development and Psychopathology, 30*(4), 1371–1317. https://doi.org/10.1017/S0954579417001602

Hedden, T., & Yoon, C. (2006). Individual differences in executive processing predict susceptibility to interference in verbal working memory. *Neuropsychology, 20*(5), 511–528. https://doi.org/10.1037/0894-4105.20.5.511

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2023). On the association between apathy and deficits of social cognition and executive functions in Huntington's disease. *Journal of the International Neuropsychological Society, 29*(4), 369–376. https://doi.org/10.1017/S1355617722000364

Hildebrandt, H., Brokate, B., Eling, P., & Lanz, M. (2004). Response shifting and inhibition, but not working memory, are impaired after long-term heavy alcohol consumption. *Neuropsychology*, *18*(2), 203–211. https://doi.org/10.1037/0894-4105.18.2.203

Husain, M., & Roiser, J. P. (2018). Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nature Reviews Neuroscience, 19*(8), 470–484. https://doi.org/10.1038/s41583-018-0029-9

J

Janssen, G. T. L., Egger, J. I. M., & Kessels, R. P. C. (2023). Impaired executive functioning associated with alcohol-related neurocognitive disorder including Korsakoff's syndrome. *Journal of Clinical Medicine, 12*(20). https://doi.org/10.3390/jcm12206477

Janssen, G., van Aken, L., de Mey, H., Witteman, C., & Egger, J. (2013). Decline of executive function in a clinical population: Age, psychopathology, and test performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB). *Applied Neuropsychology: Adult, 21*(3), 210–219. https://doi.org/10.1080/09084282.2013.793191

Jauhar, S., & Smith, I. D. (2009). Alcohol-related brain damage: not a silent epidemic. *The British Journal of Psychiatry : the Journal of Mental Science*, *194*(3), 287–288. https://doi.org/10.1192/bjp.194.3.287b

de Jonghe, J. F., Kat, M. G., Kalisvaart, C. J., & Boelaarts, L. (2003). Neuropsychiatric Inventory vragenlijstversie (NPI-Q): Validiteitsaspecten van de Nederlandse versie [Neuropsychiatric Inventory Questionnaire (NPI-Q). A validity study of the Dutch form]. *Tijdschrift voor Gerontologie en Geriatrie, 34*, 74–77.

K

Karr, J. E., Areshenkoff, C. N., Rast, P., Hofer, S. M., Iverson, G. L., & Garcia-Barrera, M. A. (2018). The unity and diversity of executive functions: A systematic review and re-analysis of latent variable studies. *Psychological Bulletin, 144*(11), 1147–1185. https://doi.org/10.1037/bul0000160

Kaufer, D. I., Cummings, J. L., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., Lopez, O. L., & DeKosky, S. T. (2000). Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *Journal of Neuropsychiatry and Clinical Neurosciences, 12*(2), 233–239. https://doi.org/10.1176/jnp.12.2.233

Kawagoe, T., Onoda, K., & Yamaguchi, S. (2017). Apathy and Executive Function in Healthy Elderly-Resting State fMRI Study. *Frontiers in aging neuroscience*, *9*, 124. https://doi.org/10.3389/fnagi.2017.00124

Kessels, R. P. C. (2019). Improving precision in neuropsychological assessment: Bridging the gap between classic paper-and-pencil tests and paradigms from cognitive neuroscience. *The Clinical Neuropsychologist, 33*(2), 357–368. https://doi.org/10.1080/13854046.2018.1518489

Kessels, R. P. C., & Kopelman, M. D. (2012). Context memory in Korsakoff's syndrome. *Neuropsychology Review, 22*(2), 117–131. https://doi.org/10.1007/s11065-012-9202-5

Kessels, R. P. C., Moerman-van den Brink, W. G., Rensen, Y. C. M., Vanma Aken, L., & Egger, J. I. M. (2021). The relation between behavioral, emotional, and cognitive apathy and everyday executive dysfunction in alcoholic Korsakoff's syndrome. *Archives of Clinical Psychiatry, 48*, 178–181. https://doi.org/10.15761/0101-60830000000301

Kessels, R. P., Kortrijk, H. E., Wester, A. J., & Nys, G. M. (2008). Confabulation behavior and false memories in Korsakoff's syndrome: role of source memory and executive functioning. *Psychiatry and Clinical Neurosciences*, *62*(2), 220–225. https://doi.org/10.1111/j.1440-1819.2008.01758.x

Khng, K. H., & Lee, K. (2014). The relationship between Stroop and stop-signal measures of inhibition in adolescents: influences from variations in context and measure estimation. *PloS one*, *9*(7), e101356. https://doi.org/10.1371/journal.pone.0101356

Klar, V. S., Ang, Y. S., Lockwood, P., et al. (2022). Assessment of apathy in neurological patients using the Apathy Motivation Index caregiver version. *Journal of Neuropsychology, 16*(1), 236–258. https://doi.org/10.1111/jnp.12262

Klauer, K. C., Schmitz, F., Teige-Mocigemba, S., & Voss, A. (2010). Understanding the role of executive control in the implicit association test: why flexible people have small IAT effects. *Quarterly Journal of Experimental Psychology (2006)*, *63*(3), 595–619. https://doi.org/10.1080/17470210903076826

Kopelman M. D. (1985). Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome. *Neuropsychologia*, *23*(5), 623–638. https://doi.org/10.1016/0028-3932(85)90064-8

Kopelman M. D. (2002). Disorders of memory. *Brain : a Journal of Neurology*, *125*(Pt 10), 2152–2190. https://doi.org/10.1093/brain/awf229

Kopelman, M. D. (1995). The Korsakoff syndrome. *The British Journal of Psychiatry, 166*(2), 154–173. https://doi.org/10.1192/bjp.166.2.154

Kopelman, M. D. (2022). What is the Korsakoff syndrome? – A paper in tribute to Prof Alwyn Lishman. *Cognitive Neuropsychiatry, 27*(4), 296–313. https://doi.org/10.1080/13546805.2022.2067472

Kopelman, M. D. (2023). Observations on the clinical features of the Wernicke-Korsakoff syndrome. *Journal of Clinical Medicine, 12*(19). https://doi.org/10.3390/jcm12196310

Kopelman, M. D., Thomson, A. D., Guerrini, I., & Marshall, E. J. (2009). The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol and alcoholism*, *44*(2), 148–154. https://doi.org/10.1093/alcalc/agn118

Korsakov Kenniscentrum. (n.d.). Hoeveel mensen in Nederland lijden aan het syndroom van Korsakov? *Korsakov Kenniscentrum*. Retrieved May 30, 2024, from https://korsakovkenniscentrum.nl/veelgestelde-vragen/hoeveel-mensen-in-nederland-lijden-aan-het-syndroom-van-korsakov

Krishnamoorthy, A., & Craufurd, D. (2011). Treatment of apathy in Huntington's disease and other movement disorders. *Current Treatment Options in Neurology, 13*(5), 508–519. https://doi.org/10.1007/s11940-011-0140-y

L

Laniepce, A., Segobin, S., Lannuzel, C., Boudehent, C., Ritz, L., Urso, L., Vabret, F., Eustache, F., Beaunieux, H., Rauchs, G., & Pitel, A. L. (2019). Neuropsychological and Neuroimaging Examinations of Self-Reported Sleep Quality in Alcohol Use Disorder With and Without Korsakoff's Syndrome. *Alcoholism, Clinical and Experimental Research*, *43*(5), 952–964. https://doi.org/10.1111/acer.13997

Lennane, K. J. (1986). Management of moderate to severe alcohol-related brain damage (Korsakoff's syndrome). *The Medical Journal of Australia, 145*(3-4), 136–143. https://doi.org/10.5694/j.1326-5377.1986.tb113772.x

Lezak, M. D. (1982). The problem of assessing executive functions. International Journal of Psychology, 17(1-4), 281–297. https://doi.org/10.1080/00207598208247445

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). Neuropsychological assessment (5th ed.). Oxford University Press.

M

Maharasingam, M., Macniven, J. A. B., & Mason, O. J. (2013). Executive functioning in chronic alcoholism and Korsakoff syndrome. *Journal of Clinical and Experimental Neuropsychology, 35*(5), 501–508. https://doi.org/10.1080/13803395.2013.795527

Marcotte, T. D., & Grant, I. (Eds.). (2010). *Neuropsychology of everyday functioning*. Guilford Press.

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-v

Maust, D. T., Langa, K. M., Blow, F. C., & Kales, H. C. (2017). Psychotropic use and associated neuropsychiatric symptoms among patients with dementia in the USA. *International Journal of Geriatric Psychiatry, 32*(2), 164–174. https://doi.org/10.1002/gps.4452

McPherson, S., Fairbanks, L., Tiken, S., Cummings, J. L., & Back-Madruga, C. (2002). Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society, 8*(3), 373–381. https://doi.org/10.1017/S1355617702813182

Meiland, F. J., Kat, M. G., Van Tilburg, W., Jonker, C., & Dröes, R. M. (2005). The emotional impact of psychiatric symptoms in dementia on partner caregivers: Do caregiver, patient, and situation characteristics make a difference? *Alzheimer Disease and Associated Disorders, 19*(4), 195–201. https://doi.org/10.1097/01.wad.0000189035.25277.02

Meyer, A., Zimmermann, R., Gschwandtner, U., Hatz, F., Bousleiman, H., Schwarz, N., & Fuhr, P. (2015). Apathy in Parkinson's disease is related to executive function, gender, and age but not to depression. *Frontiers in Aging Neuroscience, 6*, 350. https://doi.org/10.3389/fnagi.2014.00350

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science, 21*(1), 8–14. https://doi.org/10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Egger, J. I. M., & Kessels, R. P. C. (2019). Executive Dysfunction in Patients With Korsakoff's Syndrome: A Theory-Driven Approach. *Alcohol and Alcoholism*, *54*(1), 23–29. https://doi.org/10.1093/alcalc/agy078

Moerman-van den Brink, W. G., Van Aken, L., Verschuur, E. M. L., et al. (2020). The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome. *Clinical Neuropsychologist, 34*(4), 740–754. https://doi.org/10.1080/13854046.2020.1738554

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Journal of Clinical Epidemiology, 62*(10), 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

Montagne, B., Kessels, R. P. C., Wester, A. J., & de Haan, E. H. F. (2006). Processing of emotional facial expressions in Korsakoff's syndrome. *Cortex, 42*(5), 705–710. https://doi.org/10.1016/S0010-9452(08)70408-8

Muhammed, K., Ben Yehuda, M., Drew, D., Manohar, S., & Husain, M. (2021). Reward sensitivity and action in Parkinson's disease patients with and without apathy. *Brain Communications, 3*(2). https://doi.org/10.1093/braincomms/fcab022

Mulders, A. J., Fick, I. W., Bor, H., Verhey, F. R., Zuidema, S. U., & Koopmans, R. T. (2016). Prevalence and correlates of neuropsychiatric symptoms in nursing home patients with Young-Onset Dementia: The BEYOnD Study. *Journal of the American Medical Directors Association, 17*(6), 495–500. https://doi.org/10.1016/j.jamda.2016.01.002

N

Nasreddine, Z. S., Phillips, N. A., Bédirian, 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 Geriatrics Society, 53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nijsten, J. M. H., Leontjevas, R., Pat-El, R., Smalbrugge, M., Koopmans, R. T. C. M., & Gerritsen, D. L. (2017). Apathy: Risk factor for mortality in nursing home patients. *Journal of the American Geriatrics Society, 65*(10), 2182–2189. https://doi.org/10.1111/jgs.15007

Nikolakaros, G., Kurki, T., Paju, J., Papageorgiou, S. G., Vataja, R., & Ilonen, T. (2018). Korsakoff Syndrome in Non-alcoholic Psychiatric Patients. Variable Cognitive Presentation and Impaired Frontotemporal Connectivity. *Frontiers in Psychiatry*, *9*, 204. https://doi.org/10.3389/fpsyt.2018.00204

O

Oey, M. J., Brouwer, V. H. E. W., Buijs, M. J., Wijnia, J. W., Postma, A., & Oudman, E. (2021). Unraveling Apathy in Korsakoff Syndrome Patients Receiving Long-Term Care With and Without Cerebrovascular Comorbidity. *Alcoholism, Clinical and Experimental Research*, *45*(1), 131–139. https://doi.org/10.1111/acer.14513

Ornstein, K., & Gaugler, J. E. (2012). The problem with "problem behaviors": a systematic review of the association between individual patient behavioral and psychological symptoms and caregiver depression and burden within the dementia patient-caregiver dyad. *International Psychogeriatrics*, *24*(10), 1536–1552. https://doi.org/10.1017/S1041610212000737

Oscar-Berman, M. (2012). Function and dysfunction of prefrontal brain circuitry in alcoholic Korsakoff's syndrome. *Neuropsychology Review, 22*(2), 154–169. https://doi.org/10.1007/s11065-012-9198-x

Oscar-Berman, M., Kirkley, S. M., Gansler, D. A., & Couture, A. (2004). Comparisons of Korsakoff and non-Korsakoff alcoholics on neuropsychological tests of prefrontal brain functioning. *Alcoholism, Clinical and Experimental Research*, *28*(4), 667–675. https://doi.org/10.1097/01.alc.0000122761.09179.b9

Oslin, D., Atkinson, R. M., Smith, D. M., & Hendrie, H. (1998). Alcohol related dementia: proposed clinical criteria. *International Journal of Geriatric Psychiatry*, *13*(4), 203–212. https://doi.org/10.1002/(sici)1099-1166(199804)13:4<203::aid-gps734>3.0.co;2-b

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*(9), 778–781. https://doi.org/10.1016/j.jamda.2012.08.003

Oudman, E., Nijboer, T. C., 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*(2), 134–148. https://doi.org/10.1007/s11065-015-9288-7

Oudman, E., Postma, A., Nijboer, T. C. W., Wijnia, J. W., & Van der Stigchel, S. (2019). Visuospatial declarative learning despite profound verbal declarative amnesia in Korsakoff's syndrome. *Neuropsychological Rehabilitation, 29*(3), 325–338. https://doi.org/10.1080/09602011.2017.1294541

Oudman, E., Rensen, Y., & Kessels, R. P. C. (2022). Confabulations in post-acute and chronic alcoholic Korsakoff's syndrome: A cross-sectional study conducted in two centres. *International Journal of Psychiatry in Clinical Practice, 26*(2), 208–212. https://doi.org/10.1080/13651501.2021.1906907

Oudman, E., Wijnia, J. W., Oey, M., van Dam, M., Painter, R. C., & Postma, A. (2019). Wernicke's encephalopathy in hyperemesis gravidarum: A systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 236*, 84–93. https://doi.org/10.1016/j.ejogrb.2019.03.006

Oudman, E., Wijnia, J. W., Severs, D., Oey, M. J., van Dam, M., van Dorp, M., & Postma, A. (2024). Wernicke's encephalopathy in acute and chronic kidney disease: A systematic review. *Journal of Renal Nutrition, 34*(2), 105–114. https://doi.org/10.1053/j.jrn.2023.10.003

P

Packwood, S., Hodgetts, H. M., & Tremblay, S. (2011). A multiperspective approach to the conceptualization of executive functions. *Journal of Clinical and Experimental Neuropsychology*, *33*(4), 456–470. https://doi.org/10.1080/13803395.2010.533157

Palm, A., Vataja, R., Talaslahti, T., Ginters, M., Kautiainen, H., Elonheimo, H., Suvisaari, J., Lindberg, N., & Koponen, H. (2022). Incidence and mortality of alcohol-related dementia and Wernicke-Korsakoff syndrome: A nationwide register study. *International Journal of Geriatric Psychiatry*, *37*(8), 10.1002/gps.5775. https://doi.org/10.1002/gps.5775

Peirce, J. W. (2007). PsychoPy—Psychophysics software in Python. *Journal of Neuroscience Methods*, 162(1-2), 8–13.

Pitel, A. L., Beaunieux, H., Witkowski, T., Vabret, F., De La Sayette, V., Viader, F., Desgranges, B., & 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*(7), 1229–1241. https://doi.org/10.1111/j.1530-0277.2008.00677.x

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*(17), 1330–1333. https://doi.org/10.1212/WNL.0b013e318251834e

Plutchik, R., & DiScipio, W. J. (1974). Personality patterns in chronic alcoholism (Korsakoff's syndrome), chronic schizophrenia, and geriatric patients with chronic brain syndrome. *Journal of the American Geriatrics Society*, *22*(11), 514–516. https://doi.org/10.1111/j.1532-5415.1974.tb05840.x

Pollux, P. M., Wester, A., & De Haan, E. H. (1995). Random generation deficit in alcoholic Korsakoff patients. *Neuropsychologia*, *33*(1), 125–129. https://doi.org/10.1016/0028-3932(94)00095-7

Price, J., Mitchell, S., Wiltshire, B., & O'Gorman, C. (1988). A follow-up study of patients with alcohol related brain damage in the community. *Australian & New Zealand Journal of Psychiatry*, 22(1), 83–87. https://doi.org/10.1080/09595238880000191

Prigatano G. P. (2014). Anosognosia and patterns of impaired self-awareness observed in clinical practice. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *61*, 81–92. https://doi.org/10.1016/j.cortex.2014.07.014

R

Ramayya, A., & Jauhar, P. (1997). Increasing incidence of Korsakoff's psychosis in the east end of Glasgow. *Alcohol and Alcoholism*, *32*(3), 281–285. https://doi.org/10.1093/oxfordjournals.alcalc.a008268

Rensen, Y. C. M., Egger, J. I. M., Westhoff, J., Walvoort, S. J. W., & Kessels, R. P. C. (2019). The effect of errorless learning on psychotic and affective symptoms, as well as aggression and apathy in patients with Korsakoff's syndrome in long-term care facilities. *International Psychogeriatrics*, *31*(1), 39–47. https://doi.org/10.1017/S1041610218000492

Rensen, Y. C. M., Oosterman, J. M., Eling, P. A. T. M., & Kessels, R. P. C. (2023). "Cinderella was attacked by the big bad wolf, but the police saved her": intrusions and confabulations on story recall in Korsakoff's syndrome and alcohol-related cognitive impairments. *Cognitive Neuropsychiatry*, *28*(2), 85–101. https://doi.org/10.1080/13546805.2022.2153658

Rensen, Y. C., Oosterman, J. M., Walvoort, S. J., Eling, P. A., & Kessels, R. P. (2017). Intrusions and provoked and spontaneous confabulations on memory tests in Korsakoff's syndrome. *Journal of Clinical and Experimental Neuropsychology*, *39*(2), 101–111. https://doi.org/10.1080/13803395.2016.1204991

Ridley, N. J., Draper, B., & Withall, A. (2013). Alcohol-related dementia: an update of the evidence. *Alzheimer's Research & Therapy*, *5*(1), 3. https://doi.org/10.1186/alzrt157

Robert, P. H., Mulin, E., Malléa, P., & David, R. (2010). REVIEW: Apathy diagnosis, assessment, and treatment in Alzheimer's disease. *CNS Neuroscience & Therapeutics*, *16*(5), 263–271. https://doi.org/10.1111/j.1755-5949.2009.00132.x

Robert, P., Lanctôt, K. L., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., Hanon, C., David, R., Dubois, B., Dujardin, K., Husain, M., König, A., Levy, R., Mantua, V., Meulien, D., Miller, D., Moebius, H. J., Rasmussen, J., Robert, G., Ruthirakuhan, M., … Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European psychiatry : the Journal of the Association of European Psychiatrists*, *54*, 71–76. https://doi.org/10.1016/j.eurpsy.2018.07.008

Roberts, M. E., Tchanturia, K., Stahl, D., Southgate, L., & Treasure, J. (2007). A systematic review and meta-analysis of set-shifting ability in eating disorders. *Psychological Medicine*, *37*(8), 1075–1084. https://doi.org/10.1017/S0033291707009877

Roth, R. M., Isquith, P. K., & Gioia, G. A. (2005). *BRIEF-A: Behavior Rating Inventory of Executive Function—Adult Version*. Psychological Assessment Resources.

S

Sabates, J., Chiu, W. H., Loi, S., Lampit, A., Gavelin, H. M., Chong, T., Launder, N., Goh, A. M. Y., Brodtmann, A., Lautenschlager, N., & Bahar-Fuchs, A. (2024). The associations between neuropsychiatric symptoms and cognition in people with dementia: A systematic review and meta-analysis. *Neuropsychology Review, 34*(2), 581–597. https://doi.org/10.1007/s11065-023-09608-0

Salehinejad, M. A., Ghanavati, E., Rashid, M. H. A., & Nitsche, M. A. (2021). Hot and cold executive functions in the brain: A prefrontal-cingular network. *Brain Neuroscience Advances, 5*, 23982128211007769. https://doi.org/10.1177/23982128211007769

Salthouse, T. (2005). Relations between cognitive abilities and measures of executive functioning. *Neuropsychology, 19*(4), 532–545. https://doi.org/10.1037/0894-4105.19.4.532

Scalzo, S. J., & Bowden, S. C. (2023). Over a century of study and still misunderstood: Recognizing the spectrum of acute and chronic Wernicke-Korsakoff syndrome. *Journal of Clinical Medicine, 12*(21). https://doi.org/10.3390/jcm12216880

Schepers, J. P., Koopmans, R. T., & Bor, J. H. (2000). Patients with Korsakoff's syndrome in a nursing home: Characteristics and comorbidity. *Tijdschrift voor Gerontologie en Geriatrie, 31*(3), 113–118. [in Dutch]

Schmand, B., Lindeboom, J., & Van Harskamp, F. (1992). *Nederlandse Leestest voor Volwassenen: Handleiding* [Dutch Adult Reading Test: Manual]. Swets & Zeitlinger.

Selbæk, G., Engedal, K., & Bergh, S. (2013). The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: A systematic review. *Journal of the American Medical Directors Association, 14*(3), 161–169. https://doi.org/10.1016/j.jamda.2012.09.027

Senanarong, V., Poungvarin, N., Jamjumras, P., Sriboonroung, A., Danchaivijit, C., Udomphanthuruk, S., & Cummings, J. (2005). Neuropsychiatric symptoms, functional impairment, and executive ability in Thai patients with Alzheimer's disease. *International Psychogeriatrics, 17*(1), 81–90. https://doi.org/10.1017/S1041610205000980

Seppä, K., Lepistö, J., & Sillanaukee, P. (1998). Five-shot questionnaire on heavy drinking. *Alcoholism, Clinical and Experimental Research*, *22*(8), 1788–1791.

Shah, A., Herbert, R., Lewis, S., Mahendran, R., Platt, J., & Bhattacharyya, B. (1997). Screening for depression among acutely ill geriatric inpatients with a short Geriatric Depression Scale. *Age and Ageing*, *26*(3), 217–221. https://doi.org/10.1093/ageing/26.3.217

Silva, V. P. d., Carthery-Goulart, M. T., & Lukasova, K. (2024). Unity and diversity model of executive functions: State of the art and issues to be resolved. *Psychology & Neuroscience, 17*(4), 253–281. https://doi.org/10.1037/pne0000349

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology*, *6*, 328. https://doi.org/10.3389/fpsyg.2015.00328

Spearman, C. E. (1927). *The abilities of man*. Macmillan.

Starkstein, S. E., Brockman, S., Bruce, D., & Petracca, G. (2010). Anosognosia is a significant predictor of apathy in Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences, 22*(4), 378–383. https://doi.org/10.1176/jnp.2010.22.4.378

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addiction Biology*, *18*(2), 203–213. https://doi.org/10.1111/j.1369-1600.2011.00418.x

T

Talland, G. A. (1960). Psychological studies of Korsakoff's psychosis: V. Spontaneity and activity rate. *The Journal of Nervous and Mental Disease, 130*, 16–25. https://doi.org/10.1097/00005053-196001000-00003

Tate, R. L. (2010). *A compendium of tests, scales and questionnaires: The practitioner's guide to measuring outcomes after acquired brain impairments*. Psychology Press.

Tay, J., Lisiecka-Ford, D. M., Hollocks, M. J., et al. (2020). Network neuroscience of apathy in cerebrovascular disease. *Progress in Neurobiology, 188*, 101785. https://doi.org/10.1016/j.pneurobio.2020.101785

Thomson, A. D., & Marshall, E. J. (2006). The natural history and pathophysiology of Wernicke's Encephalopathy and Korsakoff's Psychosis. *Alcohol and Alcoholism*, *41*(2), 151–158. https://doi.org/10.1093/alcalc/agh249

Thomson, A. D., Guerrini, I., & Marshall, E. J. (2012). The evolution and treatment of Korsakoff's syndrome: out of sight, out of mind?. *Neuropsychology Review*, *22*(2), 81–92. https://doi.org/10.1007/s11065-012-9196-z

Tiel, C., Sudo, F., Alves, G., Ericeira-Valente, L., Moreira, D., Laks, J., & Engelhardt, E. (2015). Neuropsychiatric symptoms in vascular cognitive impairment: A systematic review. *Dementia & Neuropsychologia, 9*, 230–236. https://doi.org/10.1590/1980-57642015dn93000004

Turró-Garriga, O., Garre-Olmo, J., Vilalta-Franch, J., Conde-Sala, J. L., de Gracia Blanco, M., & López-Pousa, S. (2013). Burden associated with the presence of anosognosia in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *28*(3), 291–297. https://doi.org/10.1002/gps.3824

V

Van Aken, L., Kessels, R. P., Wingbermühle, E., van der Veld, W. M., & Egger, J. I. (2016). Fluid intelligence and executive functioning more alike than different? *Acta Neuropsychiatrica, 28*(1), 31–37. https://doi.org/10.1017/neu.2015.46

Van der Stigchel, S., Reichenbach, R. C., Wester, A. J., & Nijboer, T. C. (2012). Antisaccade performance in Korsakoff patients reveals deficits in oculomotor inhibition. *Journal of Clinical and Experimental Neuropsychology*, *34*(8), 876–886. https://doi.org/10.1080/13803395.2012.692771

van Dorst, M. E. G., Rensen, Y. C. M., Husain, M., & Kessels, R. P. C. (2021). Behavioral, emotional, and social apathy in alcohol-related cognitive disorders. *Journal of Clinical Medicine, 10*(11), 2447. https://doi.org/10.3390/jcm10112447

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

Van Oort, R., & Kessels, R. P. C. (2008). 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*(1), 78–81. https://doi.org/10.1080/13651500802308290

Victor, M. V., Adams, R. C., & Collins, G. H. (1989). *The Wernicke–Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition* (2nd ed.). F. A. Davis.

Victor, M., & Yakovlev, P. I. (1955). S.S. Korsakoff's psychic disorder in conjunction with peripheral neuritis; A translation of Korsakoff's original article with comments on the author and his contribution to clinical medicine. *Neurology, 5*(6), 394–406. https://doi.org/10.1212/wnl.5.6.394

Victor, M., Adams, R. D., & Collins, G. H. (1971). The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemporary Neurology Series*, *7*, 1–206.

Vilalta-Franch, J., Calvó-Perxas, L., Garre-Olmo, J., Turró-Garriga, O., & López-Pousa, S. (2013). Apathy syndrome in Alzheimer's disease epidemiology: Prevalence, incidence, persistence, and risk and mortality factors. *Journal of Alzheimer's Disease, 33*(2), 535–543. https://doi.org/10.3233/JAD-2012-120913

W

Walvoort, S. J. W., Wester, A. J., & Egger, J. I. M. (2013). The neuropsychology of cognitive functions in alcohol abstinence. *Tijdschrift voor Psychiatrie, 55*(2), 101–111. [in Dutch]

Walvoort, S. J., van der Heijden, P. T., Kessels, R. P., & Egger, J. I. (2016). Measuring illness insight in patients with alcohol-related cognitive dysfunction using the Q8 questionnaire: A validation study. *Neuropsychiatric Disease and Treatment, 12*, 1609–1615. https://doi.org/10.2147/NDT.S104442

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale* (4th ed.). Pearson Education.

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*(1), 134–139.

Wester, A. J., van Herten, J. C., Egger, J. I., & Kessels, R. P. (2013). Applicability of the Rivermead Behavioural Memory Test - Third Edition (RBMT-3) in Korsakoff's syndrome and chronic alcoholics. *Neuropsychiatric Disease and Treatment, 9*, 875–881. https://doi.org/10.2147/NDT.S44973

Wijnia, J. W. (2022). A clinician's view of Wernicke-Korsakoff syndrome. *Journal of Clinical Medicine, 11*(22), 6755. https://doi.org/10.3390/jcm11226755

Wijnia, J. W., Oudman, E., van Gool, W. A., Wierdsma, A. I., Bresser, E. L., Bakker, J., van de Wiel, A., & Mulder, C. L. (2016). Severe infections are common in thiamine deficiency and may be related to cognitive outcomes: A cohort study of 68 patients with Wernicke-Korsakoff syndrome. *Psychosomatics, 57*(6), 624–633. https://doi.org/10.1016/j.psym.2016.06.004

Wijnia, J. W., van de Wetering, B. J., Zwart, E., Nieuwenhuis, K. G., & Goossensen, M. A. (2012). Evolution of Wernicke-Korsakoff syndrome in self-neglecting alcoholics: preliminary results of relation with Wernicke-delirium and diabetes mellitus. *The American journal on addictions*, *21*(2), 104–110. https://doi.org/10.1111/j.1521-0391.2011.00199.x

Wilson, K., Halsey, A., Macpherson, H., et al. (2012). The psycho-social rehabilitation of patients with alcohol-related brain damage in the community. *Alcohol and Alcoholism, 47*(3), 304–311. https://doi.org/10.1093/alcalc/agr167

Y

Yeager, C. A., & Hyer, L. (2008). Apathy in dementia: Relations with depression, functional competence, and quality of life. *Psychological Reports, 102*(3), 718–722. https://doi.org/10.2466/pr0.102.3.718-722

Z

Zuidema, S. U., de Jonghe, J. F. M., Verhey, F. R. J., & Koopmans, R. T. C. M. (2009). Predictors of neuropsychiatric symptoms in nursing home patients: Influence of gender and dementia severity. *International Journal of Geriatric Psychiatry, 24*(10), 1079–1086. https://doi.org/10.1002/gps.2225

Zuidema, S. U., Derksen, E., Verhey, F. R., & Koopmans, R. T. (2007). Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *International Journal of Geriatric Psychiatry*, *22*(7), 632–638. https://doi.org/10.1002/gps.1722

Zwijsen, S. A., Kabboord, A., Eefsting, J. A., Hertogh, C. M., Pot, A. M., Gerritsen, D. L., & Smalbrugge, M. (2014). Nurses in distress? An explorative study into the relation between distress and individual neuropsychiatric symptoms of people with dementia in nursing homes. *International Journal of Geriatric Psychiatry*, *29*(4), 384–391. https://doi.org/10.1002/gps.4014

RESEARCH DATA MANAGEMENT

The studies in within this theses were pard of an external PhD studentship of the Korsakoff Center of Expertise Markenhof, Atlant (Beekbergen) and the Radboud University (Nijmegen). The research reported in this doctoral thesis followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles (findable, accessible, interoperable, reusable). The paragraphs below specify in detail how this was achieved.

ETHICS

This thesis is based on data of human participants, which were conducted in accordance with the principles of the Declaration of Helsinki. The studies in Chapters 3, 4 and 5 were approved by the by the Ethics Committee of the Faculty of Social Sciences of Radboud University (Ref. no. ECSW2015-1210-343) and the institutional review boards of Korsakoff Centre Atlant (Ref. no. mdz/mp/2015-005) and Vincent van Gogh Institute for Psychiatry (CWOP; Ref. no. 15.04365). The study in Chapter 5 was approved by the Ethics Committee of the Faculty of Social and Behavioural Sciences of Utrecht University (Ref: 20-400, 2020). All patients signed informed consent forms and when they were not legally competent, their legal representative also signed the informed consent forms. These forms were stored in the research archives of the participating healthcare organizations, separate from the data storage. They will be kept for 10 years after completion of the studies. Participant privacy was assured through the use of random individual participant IDs. Encrypted pseudonymization key files linking these participant IDs to identifiable personal information were stored on a secure network drive at the Korsakoff Center of Expertise Atlant until the research was published and then deleted. The key files were accessible only to the principal investigator associated with that study. This study in Chapter 2 was partially funded by a research grant of Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. The work was conducted as part of a larger research project, the KORSAKOFF study, which is funded by the Netherlands Organisation for Health Research and Development, Pieter van Foreest Foundation and Atlant Care Group. The study in Chapters 2, 3 and 4 were partially funded by the Topcare Foundation [Date: 2015-10-19].

FINDABLE AND ACCESSIBLE

Data cannot be shared in a public repository, because participants were not asked to consent to anonymous publication of their data at the time of informed consent, the data were stored on the secure network of the Korsakoff Center of Expertise Atlant. Paper data are stored in the research archives of the participating healthcare

institutions and will be maintained for 10 years after the completion of each study. Access to these data can be obtained by contacting the Scientific Committee of the Korsakoff Center of Expertise Atlant (onderzoek@atlant.nl).

INTEROPERABLE AND REUSABLE

Paper data are stored in their original form. Digital data were stored in IBM SPSS data files version 28.

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is om het profiel en het voorkomen van stoornissen in de executieve functies (EF) bij patiënten met het syndroom van Korsakov (KS) beter te begrijpen. Daarnaast is het onderwerp van dit proefschrift gericht op de relatie tussen de EF-stoornissen en neuropsychiatrische stoornissen, in het bijzonder apathie. In de samenvatting hieronder wordt een nederlandstalig overzicht gegeven van de belangrijkste bevindingen, gevolgd door een bespreking van theoretische en klinische overwegingen. Daarnaast worden de sterke punten en beperkingen van dit proefschrift besproken en worden klinische aanbevelingen gedaan.

SAMENVATTING

In de klinische praktijk blijkt dat zowel gedrags- als neuropsychiatrische symptomen veel voorkomen bij patiënten met KS. **Hoofdstuk 2** geeft een systematisch overzicht van eerder gepubliceerde studies met betrekking tot de prevalentie en ernst van deze symptomen bij patiënten met KS. In totaal werden vijftien studies geïncludeerd in dit systematische review. De studies laten een aanzienlijke heterogeniteit zien wat betreft hun methodologische kwaliteit, meetinstrumenten en classificatiecriteria. De hoogste prevalentiecijfers werden gerapporteerd voor depressieve symptomen en stoornissen, agitatie/agressie en psychotische symptomen en stoornissen. De hoogste ernstscores werden gevonden voor apathie. Er waren opmerkelijke verschillen tussen de artikelen in gerapporteerde prevalentie- en ernstscores van neuropsychiatrische symptomen. Geen van de geïncludeerde artikelen waren primair opgezet om de prevalentie of ernst van neuropsychiatrische symptomen bij patiënten met KS in kaart te brengen.

In **hoofdstuk 3** wordt het profiel van EF-stoornissen bij patiënten met KS beschreven. In dit onderzoek werd gebruik gemaakt van het 'unity/diversity model', zoals beschreven door Friedman en Miyake (2017). Dit model bevat drie belangrijke EF-factoren, te weten *shifting* (het kunnen schakelen tussen responsen), *updating* (het vasthouden en vernieuwen van informatie in het werkgeheugen) en *inhibition* (het onderdrukken van geautomatiseerde responsen). Om deze factoren te onderzoeken bij patiënten met KS, werden zes op maat gemaakte, gecomputeriseerde taken gebruikt die waren ontworpen om de drie factoren zo zuiver mogelijk te meten. De prestaties van 36 patiënten met KS werden vergeleken met die van 30 gezonde controles. Vergeleken met de controlegroep presteerden patiënten het slechtst op taken die shifting meten, gevolgd door

updating. Op taken die inhibition meten, verschilden de prestaties van patiënten niet significant van die van de controlegroep. Patiënten presteerden op alle taken boven kansniveau, wat aangeeft dat de taken geschikt waren voor deze cognitief beperkte doelgroep.

In **hoofdstuk 4** wordt de relatie tussen executieve disfunctie en neuropsychiatrische symptomen onderzocht bij 47 patiënten met KS. Uit het onderzoek bleek dat meer dan 85% van de patiënten met KS ten minste één neuropsychiatrisch symptoom had. De belangrijkste onderzoeksvraag was of specifieke executieve subcomponenten de variantie in neuropsychiatrische symptomen konden voorspellen. Eerst werd een factoranalyse uitgevoerd op de scores van de eerder genoemde zes taken, die de drie EF-factoren shifting, updating en inhibition meten. Hieruit werd een twee-factoren model geëxtraheerd, bestaande uit een shifting-specifieke factor en een gecombineerde updating/inhibition factor. Uit de regressieanalyse bleek dat geen van de executieve factoren de variantie in neuropsychiatrische symptomen voorspelde. Er werd wel een significante relatie gevonden tussen algemeen cognitief functioneren (zoals gemeten met de Montreal Cognitive Assessment, de MoCA) en neuropsychiatrische symptomen. Hoe ernstiger de cognitieve beperkingen, hoe meer neuropsychiatrische symptomen aanwezig zijn bij patiënten met KS.

In **hoofdstuk 5** werd op gedragsniveau gekeken naar EF-problemen van patiënten met het syndroom van Korsakov. Hiervoor werd een vragenlijst afgenomen bij informanten, namelijk de Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A). Deze vragenlijst beoordeelt EF in het dagelijks leven en bevat twee indexen: de Gedragsregulatie-index en de Metacognitie-index. De studie in dit hoofdstuk had als doel om de relatie tussen EF op gedragsniveau en apathie te onderzoeken. Apathie werd beoordeeld met behulp van de informantversie van de Apathy Evaluation Scale – Informant version (AES-I), waarbij bijzondere aandacht werd besteed aan de verschillende apathiesubtypes, namelijk gedrags-, cognitieve en emotionele apathie. In deze steekproef van 43 patiënten met KS werd 72,1% van de patiënten met KS geclassificeerd als apathisch, waarbij de hoogste scores werden gegeven op de subschalen cognitieve apathie en gedragsmatige apathie, in vergelijking met emotionele apathie. De ernst van apathie bleek gerelateerd te zijn aan metacognitieve EF-problemen, maar niet aan gedragsmatige EF-problemen. Tot slot bleek de ernst van apathie samen te hangen met algemeen cognitief functioneren, zoals gemeten met de MoCA.

Het doel van het onderzoek in **hoofdstuk 6** was om de relatie tussen EF-problemen en apathie verder te onderzoeken, rekening houdend met de veelzijdige aard van beide constructen. EF werd gemeten met behulp van drie veelgebruikte

neuropsychologische pen-en-papiertaken, een voor elke executieve factor shifting, updating en inhibition. Apathie werd beoordeeld met behulp van de informantversie van de Apathy Motivation Index (AMI). Deze vragenlijst bevat drie subschalen die apathie meten: gedragsactivatie, sociale motivatie en emotionele gevoeligheid. In een steekproef van 86 KS-patiënten kon meer dan 75% van de patiënten als apathisch worden geclassificeerd. Er was geen significant verschil in executief functioneren tussen de groep patiënten met KS die als apathisch werd geclassificeerd en de niet-apathische patiënten met KS. De apathische groep had echter een significant slechter algemeen cognitief functioneren zoals gemeten met de MoCA. Algemeen cognitief functioneren voorspelde de variantie in apathiescores, maar EF deed dat niet. Kijkend naar specifieke subdomeinen, bleken de prestaties op inhibition de variantie in sociale motivatie apathie te voorspellen.

ALGEMENE DISCUSSIE

Executief disfunctioneren bij patiënten met KS

De term “executieve functie” wordt gebruikt om het vermogen te beschrijven om het eigen gedrag, emoties en cognities te reguleren zodat iemand in staat is om regie over het eigen leven te behouden (Goldstein & Naglieri, 2014). Dit vermogen wordt in verband gebracht met zowel professionele prestaties als kwaliteit van leven (Diamond, 2013). Er is in de wetenschappelijke literatuur veel discussie over de operationalisering van dit construct en er zijn verschillende modellen voorgesteld. In dit proefschrift wordt het ‘unity/diversity model’ van Miyake en Friedman (2017) gebruikt met de drie factoren shifting, updating en inhibition om EF te onderzoeken. Het primaire doel is niet om de validiteit van het model zelf te testen, maar om de beschreven factoren te gebruiken om EF bij patiënten met KS te evalueren.

In dit proefschrift werden drie verschillende methoden gebruikt om EF te beoordelen: (1) theoriegedreven, op maat gemaakte taken die ontworpen zijn om de factoren zo zuiver mogelijk te meten; (2) klassieke neuropsychologische pen-en-papiertaken die vaak worden gebruikt in de klinische praktijk om cognitieve stoornissen te onderzoeken; en (3) gedragsvragenlijsten. Deze multimethodische benadering meet EF dus op verschillende niveaus, zowel functioneel als op het niveau van activiteiten (conform het ICF-model; World Health Organization, 2001). Dit roept de vraag op of de verschillende meetniveaus hetzelfde onderliggende concept beoordelen. Zoals vermeld in de algemene inleiding van dit proefschrift, verschillen neuropsychologische taken die EF meten in hun ecologische validiteit (dat wil zeggen de mate waarin de test het

gedrag uit het dagelijks leven weerspiegelt en voorspelt) en taakzuiverheid (dat wil zeggen de mate waarin de uitkomsten van de test worden beïnvloed door niet-executieve processen zoals taal en verwerkingssnelheid). De items in de gedragsvragenlijsten lijken het meest overeen te komen met prestaties in het dagelijks leven, terwijl de gecomputeriseerde taken zijn ontworpen om EF zo zuiver mogelijk te meten. De verschillende meetmethoden die in dit proefschrift zijn gebruikt hebben daarom verschillende doelen, voordelen en nadelen (Kessels, 2019). Het centrale doel van dit proefschrift was het onderzoeken van de ernst, het voorkomen en het profiel van EF-problemen bij patiënten met KS en de relatie met neuropsychologische symptomen. In de volgende paragrafen worden de resultaten per domein uiteengezet en worden voorlopige conclusies getrokken over executief disfunctioneren bij patiënten met KS.

Shifting (schakelen)

Uit de resultaten van dit proefschrift blijkt dat patiënten met KS aanzienlijke beperkingen hebben in hun vermogen om te schakelen. Dit betreft de vaardigheid om reeds gestelde doelen of taken te laten vervallen en vervangen door nieuwe doelen of taken als de situatie daar om vraagt. Het vermogen om te schakelen vereist ook dat men handelt in overeenstemming met dat veranderde doel of die aangepaste taak (Friedman & Miyake, 2017). Van de drie EF-factoren lijkt shifting het meest aangedaan te zijn. Deze bevinding wordt beschreven in hoofdstuk 3, waar gecomputeriseerde taken werden gebruikt, alsmede in hoofdstuk 6, waar klassieke pen-en-papier taken werden gebruikt. Zoals beschreven in hoofdstuk 3, vertoonden patiënten met KS duidelijk slechtere prestaties op beide shifting-taken dan de controlegroep, waarbij de omvang van het effect geclassificeerd kan worden als 'zeer groot'. In hoofdstuk 6 werden de prestaties van de patiënten vergeleken met een leeftijdsgecorrigeerde normgroep. De resultaten toonden aan dat meer dan 60% van de patiënten met KS meer dan 1,5 standaarddeviatie (SD) lager scoorde dan de normgroep. Dit percentage is hoger dan het percentage patiënten dat beperkingen had in de EF-factoren updating (43%) en inhibition (32%). Verder bleek dat patiënten bij de shifting taken gemiddeld meer tijd nodig hadden en meer fouten maakten dan de normgroep. Het vermogen om te schakelen bleek ook aangetast te zijn op gedragsniveau, zoals gerapporteerd door zorgverleners in de BRIEF-A subschaal die flexibiliteit meet. De onderliggende items van deze schaal hebben bijvoorbeeld betrekking op problemen met de overgang van de ene activiteit naar de andere, de uitdaging om te accepteren dat oplossingen voor problemen kunnen variëren, het vermogen om zich aan te passen aan veranderingen en de neiging om van streek te raken als er onverwachte

veranderingen optreden in iemands dagelijkse routine. Gemiddeld genomen vielen de resultaten van patiënten in deze subschaal in het klinisch gestoorde bereik.

"Ik ben nogal star als ik mijn bed uit moet. Dan moeten ze me echt met drie man mijn bed uit trekken. Ik heb er wel een beetje moeite mee. Ik heb het gevoel dat je hier dingen moet doen tegen je zin in." – Vrouw met KS, 56 jaar

"Heel veel mensen hier, daar zal ik ongetwijfeld bij horen, zijn heel erg gebaat zijn bij een dagindeling, die maak je er niet blij mee als dat plotseling verandert." – Man met KS, 67 jaar

Updating (werkgeheugen)

De EF-factor 'updating' is in wisselende mate aangedaan bij patiënten met KS, blijkt uit metingen met neuropsychologische taken. In Hoofdstuk 3 presteerden KS-patiënten gemiddeld significant slechter dan controles op taken die de updating meten, de omvang van dit effect kan geclassificeerd worden als 'groot'. De effectgroottes verschilden tussen non-verbale en verbale updatingstaken, waarbij de laatste gemiddeld het ernstigst aangedaan was bij patienten met KS. Hoofdstuk 6 laat zien dat 43% van de patiënten meer dan 1,5 SD onder het normatieve gemiddelde presteerde op de subtest Cijferreeksen van de Wechsler Adult Intelligence Scale - Fourth edition (WAIS-IV). Volgens Friedman en Miyake (2017) vereist updating de constante vervanging van informatie in het werkgeheugen en is het dus nauw verwant aan het construct van het werkgeheugen, waarbij het ook gaat om het manipuleren van die informatie die in het werkgeheugen vastgehouden wordt. Updating wordt vaak geoperationaliseerd met taken die het werkgeheugen beoordelen. Eerder onderzoek toont aan dat het werkgeheugen is aangetast bij patiënten met KS (van Geldorp et al., 2011; Arts et al., 2017; Pitel et al., 2009; Eikelboom et al., 2024; Oudman et al., 2019). De resultaten van dit proefschrift bevestigen deze bevindingen en geven meer inzicht in het voorkomen en de ernst van werkgeheugenproblemen bij patiënten met KS. Op gedragsniveau werd werkgeheugen gemeten met de subschaal Werkgeheugen van de BRIEF-A. De gemiddelde scores op deze subschaal werd geclassificeerd als klinisch aangedaan. De onderliggende items betreffen onder andere de problemen met concentratie, het voltooien van taken, het vasthouden van focus in een gesprek, het kortetermijngeheugen en multitasking.

"Ik heb moeite met overzicht houden. Ik heb wel echt een agenda nodig, dat vind ik wel fijn. Ik wil wel weten waar ik aan toe ben." – Man met KS, 67 jaar

Inhibition (inhibitie)

De resultaten van het onderzoek in hoofdstuk 3 suggereren dat het inhibitievermogen slechts beperkt is aangedaan bij patienten met KS. Het inhibitievermogen werd gemeten met behulp van een verbale en een non-verbale computertaak. Bij deze taken moesten patiënten stimuli categoriseren, waarbij de categorisatieregels tijdens de taak veranderden, waardoor de patiënt gedwongen werd om hun aangeleerde automatische reactie te inhiberen. In beide taken presteerden de KS-patiënten boven kansniveau en hun gemiddelde prestaties verschilden niet significant van die van de controlegroep. De patiënten waren echter significant trager in hun categorisatieproces en maakten significant meer fouten dan de controlegroep. In hoofdstuk 6 werd het inhibitievermogen beoordeeld met een variant van de Stroop-test, de Color Word Interference Test (CWIT) van het Delis-Kaplan Executive Function System. Vergeleken met de leeftijdsgecorrigeerde normgroep presteerde ongeveer een derde van de patiënten meer dan 1,5 SD onder het normatieve gemiddelde op de inhibitieconditie, wat duidt op een verminderde prestatie. Opmerkelijk was dat slechts 7,3% van de patiënten scores liet zien die meer dan 1,5 SD onder het normatieve gemiddelde lagen toen de contrastscore werd berekend. Op gedragsniveau was de gemiddelde score op de subschaal Inhibitie van de BRIEF-A niet klinisch afwijkend. Deze subschaal identificeert gedrag zoals moeite hebben met wachten of stilzitten, ongepaste seksuele opmerkingen maken, snel afgeleid zijn of impulsief handelen. De resultaten van dit proefschrift geven aan dat problemen met inhibitie geen prominent kenmerk zijn van KS. Dit staat in contrast met eerder onderzoek dat inhibitieproblemen rapporteerde bij patiënten met KS met behulp van gecomputeriseerde taken (Janssen et al., 2023; El Haj et al., 2020). Deze verschillen in resultaten kunnen mogelijk worden toegeschreven aan variaties in de gebruikte taken en het type uitkomstmaat dat wordt gebruikt om inhibitie te beoordelen. In tegenstelling tot de conclusie dat inhibitieproblemen geen prominent kenmerk zijn van KS, worden er in de klinische praktijk veel gedragingen waargenomen die kunnen duiden op inhibitieproblemen. Denk hierbij aan agressie en agitatie, seksueel ongepast gedrag, ontremd eten, roken en overmatig gebruik van koffie of frisdrank. Het is denkbaar dat dit soort gedragsproblemen weliswaar niet veelvoorkomend zijn, maar desondanks een enorme belasting zijn voor zorgverleners, en dat dit veel aandacht vraagt van het multidisciplinaire behandelteam, ook als dit bij slechts een paar patiënten op de afdeling voorkomt.

"Ik heb een robotkat gekregen, daar speel ik graag mee. Nu heb ik moeite om dat soms niet te doen, ook 's nachts. Nu hebben ze de batterij eruit gehaald. Dan gaat een ander mij dus afremmen en dat vind ik niet zo leuk." – Vrouw met KS, 56 jaar

"Ik eet gewoon door."– Man met KS, 77 jaar

Executieve functiestoornissen en basale cognitieve vaardigheden

In de neuropsychologische taken die in hoofdstuk 3 en 6 werden gebruikt voor zowel schakel- als inhibitievermogen, diende reactietijd als uitkomstmaat, waarmee vervolgens een contrastscore berekenend werd. Deze contrastscore geeft het verschil in reactietijd aan tussen vergelijkbare taakcondities met en zonder een executieve (dat wil zeggen shifting, inhibition) component (vgl. Donders, 1868/1969). Met andere woorden; het gebruik van een contrastscore vergemakkelijkt het onderscheid tussen de executieve aspecten van een gegeven taak en de onderliggende cognitieve processen, zoals verwerkingssnelheid en taalvaardigheid. KS-patiënten presteerden op alle taakcondities trager, dus zowel bij de executieve condities, maar ook bij de baseline condities, vergeleken met gezonde controles (hoofdstuk 3) of met een leeftijdsgecorrigeerde normgroep (hoofdstuk 6). Verder bleek dat als reactietijd op de exeuctieve condite als uitkomstmaat genomen werd, in plaats van de contrastscore, een hoger percentage KS-patiënten beneden de 1,5 SD onder het normatieve gemiddelde presteerde (60,7% versus 13,1% voor shifting en 32,9% versus 7,3% voor inhibition). Dit bevestigt dat snelheidsverschillen minimaal terug te vinden zijn in de uiteindelijke resultaten van de executieve taken. Desalniettemin is de zinvolheid van deze berekening bij ernstige problemen met deze basale cognitieve vaardigheden discutabel. Het is namelijk denkbaar dat mensen die al aanzienlijk vertraagd reageren, minder extra tijd nodig hebben om te schakelen of te inhiberen, wat resulteert in een kleinere en dus minder afwijkende contrastscore. Dit zou de indruk kunnen wekken van optimale EF, ondanks dat deze score voornamelijk wordt beïnvloed door de basale cognitieve vaardigheden, in plaats van daadwerkelijk 'hoger-orde' EF (zie ook Biesmans et al., 2018).

Executieve functiestoornissen in de context

In dit proefschrift wordt een multimethodische aanpak gebruikt om de mate van EF-problemen bij patiënten met KS te onderzoeken, waaronder verschillende neuropsychologische testen en gedragsvragenlijsten. Een significant deel van de personen met KS presteerde binnen de gemiddelde range op testniveau, een bevinding die overeenkomt met de klinische praktijk, waar het regelmatig voorkomt dat executieve testresultaten bij KS-patiënten niet afwijkend zijn. Echter,

in diezelfde klinische praktijk worden regelmatig diverse problemen waargenomen die geassocieerd kunnen worden met EF-problemen, zoals initiatiefproblemen en moeite met het organiseren van dagelijkse activiteiten. Bovendien verbleven de patiënten met KS die deelnamen aan dit onderzoek in instellingen en waren ze afhankelijk van 24-uurs zorg. De meerderheid van hen had een formele of informele vertegenwoordiger om namens hen beslissingen te nemen (Gerridzen & Goossensen, 2014), wat indicatief kan zijn voor EF-problemen. Het is belangrijk op te merken dat het opsporen van EF-problemen bij patiënten met KS een uitdaging is en dat de context van de beoordeling de verkregen resultaten kan beïnvloeden. Zo wordt de mate van EF-problemen die worden waargenomen bij neuropsychologisch onderzoek beïnvloed door de keuze van de test en de gebruikte uitkomstmaat, zoals hierboven besproken. Daarnaast is de context van invloed op de rapportage van EF-problemen op gedragsniveau. In een gestructureerde omgeving die wordt gekenmerkt door de aanwezigheid van veel zorg, zijn EF-problemen mogelijk minder opvallend dan in een omgeving waar hoge eisen worden gesteld aan EF-vaardigheden. Daarmee is de precieze invloed van de context bij het in kaart brengen van EF-problemen een belangrijk gebied voor verder onderzoek naar EF-problemen bij mensen met KS.

Executive functiestoornissen en neuropsychiatrische symptomen (met name apathie)

Een belangrijke reden om de EF van patiënten met KS in kaart te brengen, is omdat verondersteld wordt dat EF-problemen samenhangen met gedragsproblemen of neuropsychiatrische symptomen. Neuropsychiatrische symptomen zijn veelvoorkomend bij mensen met KS. Uit onderzoek blijkt dat bij patiënten met KS die in verpleeghuizen verblijven, 96,4% ten minste 1 neuropsychiatrisch symptoom, en bijna de helft (45,8%) 5 of meer symptomen heeft (Gerridzen et al., 2018). De aanwezigheid van neuropsychiatrische symptomen draagt bij aan de ervaren zorglast in deze populatie. Een van de meest prominente neuropsychiatrische symptomen bij patiënten met KS is apathie. In dit proefschrift werd driekwart van de patiënten geclassificeerd als apathisch (zie hoofdstukken 4, 5 en 6). Apathie wordt omschreven als een stoornis in de motivatie, die zich manifesteert als een afname in doelgerichte activiteit ten opzichte van het eerdere niveau van functioneren. Apathie wordt geconceptualiseerd als een veelzijdig syndroom (Kos et al., 2016) met verschillende subtypes, te weten gedragsmatige, emotionele en sociale apathie (Robert et al., 2018; Ang et al., 2017). Apathie kan worden gemeten door zelfrapportage of door observatie, zoals de Apathy Evaluation Scale (AES). De AES werd gebruikt in dit proefschrift, maar deze is ontworpen om apathie te meten als een unitair construct. Daarom werd in dit proefschrift ook een recent

ontwikkelde vragenlijst gebruikt, de Apathy Motivation Index (AMI). De AMI is een multidimensioneel instrument dat tot doel heeft subtypes van apathie te identificeren, waaronder gedragsmatige, sociale en emotionele apathie.

Een van de centrale vragen van dit proefschrift betreft de relatie tussen EF-problemen van mensen met KS en de neuropsychiatrische symptomen, met een speciale focus op apathie. In dit proefschrift werden de volgende bevindingen gedaan: Er werd een significant verband gevonden tussen de Apathy Evaluation Scale (AES) en de BRIEF-A Metacognitieschaal. Wat betreft de neuropsychologische EF taken bleek dat er geen significante relatie was tussen de Neuropsychiatric Inventory - Questionnaire (NPI-Q) en gecomputeriseerde EF-taken. Bovendien werd er geen significante relatie waargenomen tussen de Apathy Motivation Index (AMI) en drie EF-taken op papier en potlood. Er werd echter wel een significante correlatie gevonden tussen de AES, de NPI-Q en de AMI met algemeen cognitief functioneren, zoals gemeten met de Montreal Cognitive Assessment (MoCA). De bevindingen suggereren dat voornamelijk algemeen cognitief functioneren verband houdt met de prevalentie van neuropsychiatrische symptomen en apathie.

Het verband tussen EF-problemen en neuropsychiatrische symptomen is ook onderzocht bij verschillende neurodegeneratieve aandoeningen. In een review van onderzoeken naar cognitieve correlaten van neuropsychiatrische symptomen bij patiënten met de ziekte van Parkinson werden verbanden gevonden tussen executieve disfunctie en neuropsychiatrische symptomen, waaronder apathie (Alzahrani & Venneri, 2015). Een recente review en meta-analyse vond een verband tussen neuropsychiatrische symptomen en verslechterd algemeen cognitief functioneren en EF-problemen bij mensen met verschillende soorten dementie (Sabates et al., 2023). Veel van de studies die in beide reviews werden geïncludeerd, vonden echter geen verband tussen EF en neuropsychiatrische symptomen. Een verklaring is dat wanneer deze relatie wordt onderzocht in patiëntengroepen, de relatieve variabiliteit van zowel EF-problemen als neuropsychiatrische symptomen klein is, waardoor het moeilijk is om onderliggende relaties te detecteren. Daarnaast wordt de aanwezigheid van neuropsychiatrische symptomen waarschijnlijk bepaald door een veelheid aan factoren, waaronder biologische, psychologische, sociale en cognitieve elementen (Sabates et al., 2023). De eerder genoemde onderzoeken hebben zich voornamelijk gericht op het isoleren van cognitieve factoren, het huidige proefschrift richt zich op dezelfde manier uitsluitend op het beoordelen van de cognitieve correlaten van neuropsychiatrische symptomen. De relatieve invloed van andere factoren bepaalt ook de sterkte van de gevonden relatie tussen EF en neuropsychiatrische symptomen.

Concluderend kan gesteld worden dat de aanwezigheid van neuropsychiatrische symptomen en de ernst van apathie bij patiënten met KS verband houdt met de ernst van het algemeen cognitief disfunctioneren. Hoe ernstiger de cognitieve problemen, hoe meer uitgesproken de neuropsychiatrische symptomen en apathie.

AANBEVELINGEN VOOR ONDERZOEK EN KLINISCHE PRAKTIJK

Patiënten met KS vormen een heterogene groep waarbij de ernst van de cognitieve stoornissen varieert, met wisselende comorbide somatische en psychiatrische aandoeningen. Deze patiënten zijn vaak zorgmijdend en beschikken meestal over een beperkt sociaal netwerk. Hierdoor wordt het stellen van de juiste diagnose vaak bemoeilijkt door de afwezigheid van cruciale (door informanten geverifieerde) informatie. Bij de selectie van de deelnemers in dit proefschrift was het de bedoeling om patiënten met bijkomende hersenaandoeningen, zoals een hersentumor, traumatisch hersenletsel of neurodegeneratieve pathologie (bijv. cerebrovasculaire pathologie of de ziekte van Alzheimer), uit te sluiten. Echter bij veel patiënten die in een verpleeghuis verblijven, werd de oorspronkelijke diagnose KS jaren voor de inclusie in dit onderzoek gesteld. Vanwege de bovengenoemde uitdagingen kan niet worden uitgesloten dat sommige patiënten met comorbide neuropathologie zijn geïncludeerd. Daarnaast bestaat er tot op heden geen consensus over diagnostische criteria voor KS (Arts et al., 2017). Dit is een belangrijk obstakel voor het diagnostisch proces in de klinische praktijk, maar draagt ook bij aan de heterogeniteit van de onderzoeksgroep. Het wordt daarom aanbevolen om internationale consensus te bereiken over het gebruik van neuropsychologische testen in het diagnostisch proces en het vaststellen van goed gedefinieerde diagnostische criteria.

KS is een aandoening die zeer gespecialiseerde zorg en behandeling vereist, met een lage incidentie in de algemene bevolking (zie ook Palm et al., 2022). Binnen de Nederlandse gezondheidszorg is KS een van de patiëntenpopulaties die door het Nederlandse Ministerie van Volksgezondheid zijn aangewezen als “Laag Volume, Hoog Complex” (LVHC). In de wetenschappelijke literatuur zien we deze lage prevalentie weerspiegeld in de typische steekproefgrootte van onderzoeken naar KS, vaak bestaand uit 10-20 patiënten. Dergelijke kleine steekproeven vergroten de kans op toevalsbevindingen, veroorzaakt door uitschieters als gevolg van co-morbiditeit of andere verstorende factoren (dat wil zeggen een Type I fout). Bovendien resulteren kleine steekproeven ook in een lage statistische power,

waardoor de kans op een Type II fout toeneemt. De zorgstructuur van de LVHC-patiënten met een landelijk kennisnetwerk (het Korsakov Kenniscentrum; www.korsakovkenniscentrum.nl) faciliteert de samenwerking tussen de gespecialiseerde instellingen in zowel de geestelijke gezondheidszorg als de langdurige zorg. Daarom wordt, zoals aangetoond met dit proefschrift, de inclusie van een groter cohort patiënten haalbaar geacht. Bij andere LVHC-patiëntenpopulatieszoals patiënten met de ziekte van Huntington of traumatische hersenletsel worden ook EF-stoornissen gevonden. Vervolgonderzoek kan zich richten op het vergelijken van de EF-stoornissen bij de eerder genoemde patiëntengroepen om te onderzoeken of er specifieke executieve disfunctieprofielen zijn bij de verschillende stoornissen.

Het gebruik van neuropsychologische testen die executieve functies meten bij patiënten met ernstige cognitieve stoornissen is complex. Naast de eerder genoemde problemen met taakzuiverheid en ecologische validiteit, laten de bevindingen van dit proefschrift zien dat veel mensen met KS een beperkte verwerkingssnelheid hebben, wat ertoe kan leiden dat niet aan de taakvoorwaarden wordt voldaan. Dit is met name relevant voor taken waarbij reactiesnelheid een component is van de eindscore, zoals eerder besproken. Daarom wordt aanbevolen om rekening te houden met deze beperkingen bij het interpreteren van de testresultaten. Het opnemen van observationele vragenlijsten in neuropsychologisch onderzoek wordt aanbevolen, maar kent ook inherente beperkingen. Veel patiënten verblijven ten tijde van een neuropsychologisch onderzoek in een instelling. Hierdoor zijn sommige onderdelen van de observationele EF-vragenlijsten niet altijd passend bij de dagelijkse activiteiten van de patiënt. Ter illustratie: de meerderheid van de patiënten in instellingen hoeft geen maaltijden te bereiden en wordt aangemoedigd om zich te houden aan het vastgestelde schema van hun dagelijkse activiteiten. Daardoor is het moeilijk om vast te stellen in hoeverre patiënten deze vaardigheden bezitten. Bovendien bestaat de kans op vertekening door observatie. Meestal worden gedragsobservatielijsten ingevuld door zorgverleners, die geneigd kunnen zijn om de prestaties van verschillende patiënten met elkaar te vergelijken in plaats van met gezonde controles. Afhankelijk van het gebruikte referentiekader, kunnen de capaciteiten van de patiënt dus worden overschat. Het wordt aanbevolen om de beoordeling van EF-stoornissen niet te beperken tot neuropsychologische testresultaten, maar ook andere meetniveaus op te nemen, zoals gedragsvragenlijsten, naast observatie- en interviewgegevens.

LEVEN MET EXECUTIEVE FUNCTIESTOORNISSEN

Een aanzienlijk deel van de patiënten met KS verblijft in instellingen voor langdurige zorg. Als onderdeel van dit proefschrift werd een groep patiënten die in het Korsakoff Expertisecentrum Markenhof van Atlant verblijven, geïnterviewd over hun ervaringen met EF-problemen. Veel patiënten met KS hebben een beperkt of afwezig ziekte-inzicht in hun ziekte, wat hun perceptie van EF-problemen beïnvloedt. In dit interview werd opgemerkt dat sommige patiënten desalniettemin in staat waren om ten minste enkele van de besproken problemen te herkennen, hetzij bij zichzelf of bij hun medebewoners. Een belangrijke vraag in de klinische praktijk betreft het vinden van een geschikte behandeling voor EF-stoornissen. Zoals een patiënt zei: "*Het is een heel belangrijk onderwerp, omdat het zo fundamenteel is. Ik heb ook geleerd dat het niet zo is dat je het niet meer kunt leren. Als je het hebt over het syndroom van Korsakov, heb je het over 20 tinten grijs.*" De vraag naar training of behandeling komt ook van verpleegkundigen, verzorgenden en andere zorgverleners. In de afgelopen decennia zijn specifieke methodologieën ontwikkeld voor mensen met KS, waaronder foutloos leren en de empathisch-directieve benadering. Een van de belangrijkste uitdagingen voor zorgverleners van mensen met KS is het omgaan met gedragsproblemen. Hoewel deze gedragsproblemen samengaan met cognitieve stoornissen, blijkt dat de aanwezigheid en ernst van neuropsychiatrische symptomen niet alleen kan worden voorspeld op basis van EF-problemen. Bovendien speelt de fysieke en sociale omgeving een cruciale rol bij het beïnvloeden van het ontstaan en de intensiteit van gedragsproblemen. Het concept van gedrag is uitgebreider en omvat meer dan alleen neuropsychiatrische symptomen. Er is momenteel geen specifieke behandeling beschikbaar voor EF-stoornissen bij KS. Omdat de beschadiging in het brein bij mensen met KS onomkeerbaar is, richten behandelingen zich op het vergroten van functioneren, de (ervaren) autonomie en kwaliteit van leven. In de zorg voor mensen met KS is specifieke aandacht nodig voor EF-problemen. Het wordt aanbevolen om de fysieke en sociale omgeving zo te ontwerpen dat er zo min mogelijk eisen worden gesteld aan vaardigheden zoals flexibiliteit, het vermogen om gedrag te remmen en het werkgeheugen. Over het algemeen hebben mensen met KS baat bij een gestructureerde dagelijkse routine, vaste activiteiten en een voorspelbare omgeving. Daarnaast is specifieke, multidisciplinaire behandeling van patiënten nodig om problematisch gedrag aan te pakken, deelname van patiënten aan activiteiten aan te moedigen en gezonde routines te bevorderen (van Dorst et al., 2024). Zoals een patiënt zei: *"Onderzoek hiernaar moet heel veel opleveren. Wat kan er gedaan worden voor mensen met het syndroom van Korsakov? Moeten we ze ergens bij helpen? Kunnen we ze helpen? En daar moeten we niet mee wachten."*

CURRICULUM VITAE

Wiltine van den Brink werd op 23 december 1988 geboren in Ede. Nadat zij in 2007 haar VWO-diploma behaalde aan de Jacobus Fruytier scholengemeenschap in Apeldoorn, begon ze aan de opleiding Psychologie aan de Radboud Universiteit in Nijmegen. Na afronding van haar bachelor koos ze voor de master Gezondheidszorgpsychologie aan diezelfde universiteit. Na het behalen van haar masterdiploma in 2011 is ze gestart als masterpsycholoog bij Atlant, een organisatie in de langdurige zorg die zich richt op specifieke doelgroepen, waaronder mensen met het syndroom van Korsakov. Naast haar werk als psycholoog startte zij in 2014 als buitenpromovendus bij het Donders Instituut van de Radboud Universiteit, waarvan dit proefschrift het resultaat is. In 2023 voltooide zij bij Atlant de postmasteropleiding tot gezondheidszorg-psycholoog en in 2025 is ze gestart met de specialistische vervolgopleiding tot klinisch neuropsycholoog bij Tactus verslavingszorg in Zutphen.

LIST OF PUBLICATIONS

Rinck, M., Koene, M., Telli, S., Moerman-van den Brink, W., Verhoeven, B., & Becker, E. S. (2016). The time course of location-avoidance learning in fear of spiders. *Cognition & Emotion*, *30*(3), 430–443. https://doi.org/10.1080/02699931.2015.1009873

Gerridzen, I. J., Moerman-van den Brink, W. G., Depla, M. F., Verschuur, E. M. L., Veenhuizen, R. B., Wouden, J. C., Hertogh, C. M. P. M., & Joling, K. J. (2017). Prevalence and severity of behavioural symptoms in patients with Korsakoff syndrome and other alcohol-related cognitive disorders: A systematic review. *International Journal of Geriatric Psychiatry, 32*(3), 256–273. https://doi.org/10.1002/gps.4636

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Egger, J. I. M., & Kessels, R. P. C. (2018). Executive dysfunction in patients with Korsakoff's syndrome: A theory-driven approach. *Alcohol & Alcoholism, 54*(1), 23–29. https://doi.org/10.1093/alcalc/agy078

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Rensen, Y. C. M., Egger, J. I. M., & Kessels, R. P. C. (2020). The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome. *The Clinical Neuropsychologist, 34*(4), 740–754. https://doi.org/10.1080/13854046.2020.1738554

Kessels, R. P. C., Moerman-van den Brink, W. G., Rensen, Y. C. M., van Aken, L., Walvoort, S. J. L., & Egger, J. I. M. (2021). The relation between behavioral, emotional and cognitive apathy and everyday executive dysfunction in alcoholic Korsakoff's syndrome. *Archives of Clinical Psychiatry, 48*(3), 178–181. https://doi.org/10.15761/0101-60830000000301

Moerman-van den Brink, W. G., Oey, M. J., van Aken, L., Oudman, E., Postma, A., Egger, J. I. M., & Kessels, R. P. C. (in preparation). *Is executive dysfunction associated with apathy in patients with alcoholic Korsakoff's syndrome?*

Oey, M. J., Moerman-van den Brink, W. G., Postma, A., Kessels, R. P. C., & Oudman, E. (in press). Apathy in Korsakoff's Syndrome: a call for clinical awareness in long-term care settings. *Journal of the American Medical Directors Association*.

DONDERS GRADUATE SCHOOL

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 750 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher

education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit:

http://www.ru.nl/donders/graduate-school/phd/

9 789465 151373 >

atlant

korsakov
kenniscentrum

alles over korsakov

DONDERS INSTITUTE

Radboud University

Radboudumc