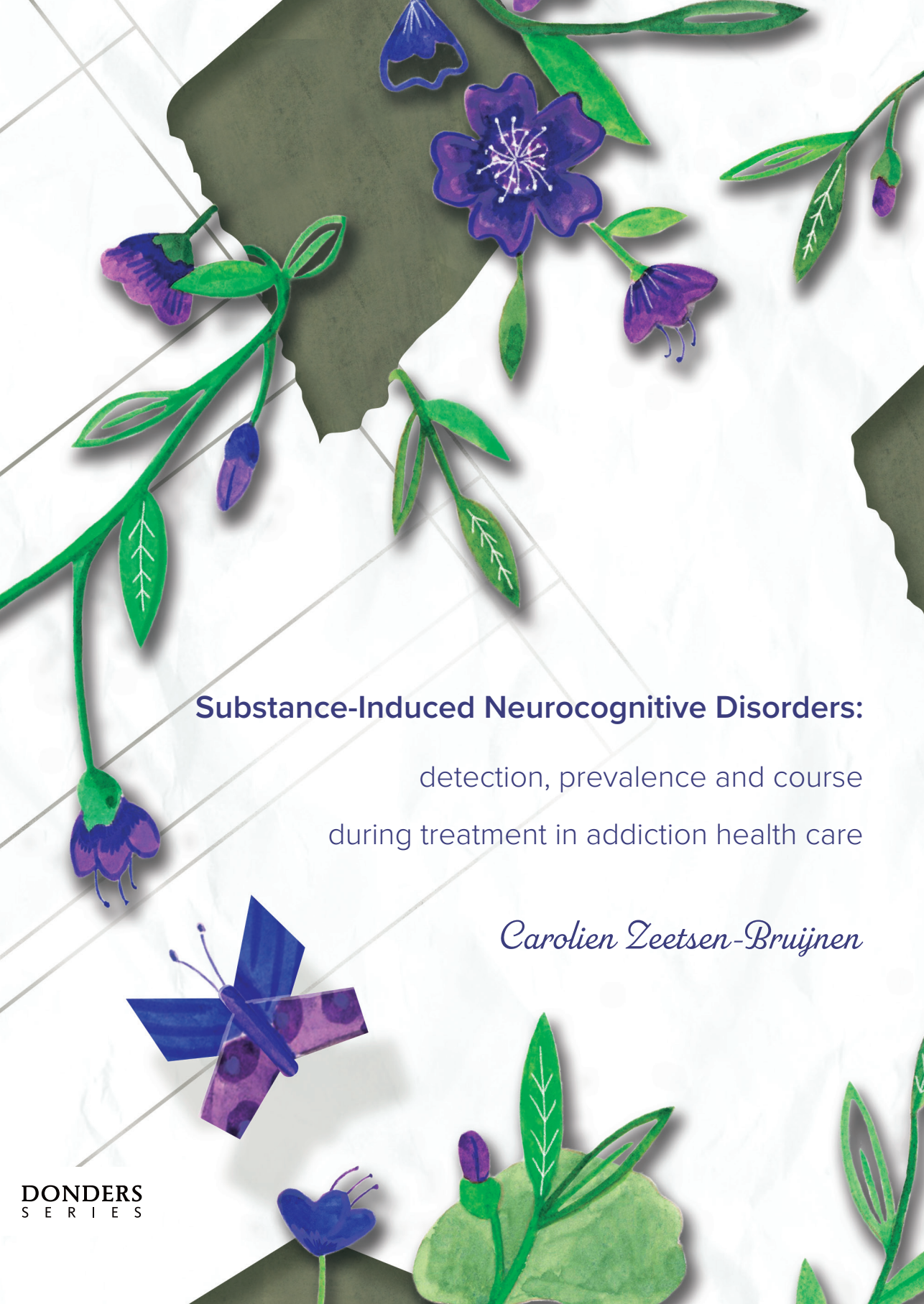

# Substance-Induced Neurocognitive Disorders:

## detection, prevalence and course during treatment in addiction health care

*Carolien Zeetsen-Bruijnen*

DONDERS
SERIES

# Substance–Induced Neurocognitive Disorders:

DETECTION, PREVALENCE AND COURSE DURING TREATMENT IN ADDICTION HEALTH CARE

Carolien Zeetsen–Bruijnen

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**The public defence of this thesis was postponed until**

**19 February 2021**

# Substance–Induced Neurocognitive Disorders:

DETECTION, PREVALENCE AND COURSE DURING TREATMENT IN ADDICTION HEALTH CARE

**[Neurocognitieve stoornissen door een middel:
detectie, prevalentie en behandelverloop]**

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op
vrijdag 4 december 2020,
om 11.30 uur precies

door

Carolien Josephina Wilhelmina Hermina Zeetsen–Bruijnen
geboren op 27 juni 1985
te Maasbree

| | |
|---|---|
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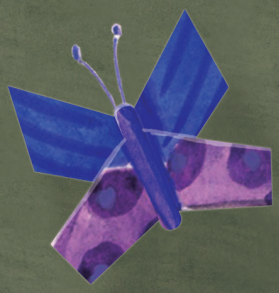
Voor Jeste, mijn ‘goudlokje’

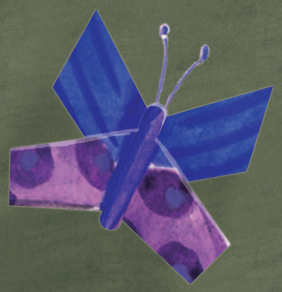
‘We almost never think of the present,
and when we do,
it is only to see what light it throws
on our plans for the future.’

António R. Damasio



# Table of contents

Met wie begin je je dankwoord... ik roep altijd dat ik in de eerste plaats moeder en vrouw ben, daarna komt de rest. Koos, ik wil daarom beginnen met jou te eren, eren dat je het al die jaren met mij en mijn last–minute–stress hebt volgehouden. Eren dat je nog steeds van me houd zoals ik ben, met al mijn chaos en eigenaardigheden. Eren dat jij, terwijl ik dus riep dat jullie vooraan stonden, maar vervolgens vele uren vrije tijd besteedde met mijn laptop op schoot, jij grotendeels het huishouden runde, mij in bedwang hield als ik weer hormonale nukken had, en (ondanks een ruzietje of twee) altijd achter me bleef staan. En ik wil jou bedanken, bedanken voor wat we samen bereikt hebben, samen met Jeste en ons 'boontje' (wat ben ik blij dat ook hij/zij op komst is!!) zijn jullie mijn leven, mijn steun, mijn alles. Zonder jullie had ik dit nooit af kunnen ronden. Zoals beloofd heb ik vanaf nu weer (alle?) tijd voor jullie. Ik hou van jullie!



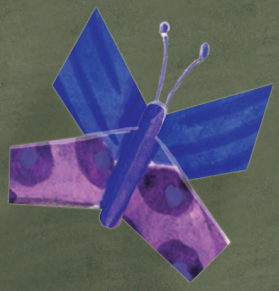
# Dankwoord

# Dankwoord




Waar begin je het dankwoord mee... Van alle proefschriften die ik onder ogen heb gekregen, bladerde ik vrijwel meteen naar achteren voor het dankwoord (en daarna de Nederlandse samenvatting). Waarom? Waarschijnlijk om een stukje inspiratie op te doen zodat ik mijn eigen weg als promovenda door het leven van gezin, familie, vrienden en carrière weer eventjes kon blijven bewandelen. In sommige gevallen om erkenning te krijgen, want het is en blijft leuk om je eigen naam in iemand anders zijn meesterwerk terug te zien in de wetenschap dat je een klein steentje hebt kunnen bijdragen. In de meeste gevallen toch, omdat het mij vaak meenam in het proces wat 'promotieonderzoek' heet. De herkenning dat anderen ook worstelden met de 'balans' en dat het doen van promotieonderzoek voor vrijwel iedereen een persoonlijke levensreis is. Ik ben daarom mijn proefschrift letterlijk begonnen met het dankwoord. Al is het enkel al om iedereen te misleiden want ik houd wel van een grapje! Hoeveel van jullie hebben eerst naar het einde van het boekje gebladerd? Haha! Zoals voor mij het doen van promotieonderzoek en het schrijven van dit proefschrift een hele klus was, zo wordt dat voor jullie het lezen van het volledige dankwoord!

Bedankt ook aan mijn promotoren, Roy en Cor, en co–promotoren, Arie, Serge en Boukje. Arie, ik begin bij jou, want aan jou heb ik voor mijn gevoel alles rondom deze mijlpaal te danken. Helaas kun je me nu niet zien stralen en kan ik je niet stilzwijgend in de deuropening zien staan. Maar je bent er zeker bij geweest, dit hele proces, en in gedachten zie ik je jouw 'goedkeurende knikje' geven. Je wordt gemist! Cor, ook jij hebt de potentie in mij gezien en mij de kans gegeven te ontdekken dat ik onderzoek doen eigenlijk toch wel leuk vind. Bedankt voor die kans en bedankt ook voor alle wijze woorden en inspiratie. Roy, jouw wijze woorden (en perfecte zinnen die je zo uit je mouw leek te schudden, waar ik een eeuwigheid over gedaan had, net zoals deze...), adviezen, snelle denken en directe handelen hebben mij inspiratie gegeven. Inspiratie die ik soms super hard nodig had. Je moet zeker met momenten gedacht hebben 'als dat maar goed komt', hopelijk heb ik je een beetje trots kunnen maken. Serge, als niets–wetende stagiaire (zo voelde ik mij althans) heb jij me begeleid in de start van mijn klinische carrière. Ik heb me thuis gevoeld in de Korsakov, mede door jouw vertrouwen. Tot slot Boukje, je kwam onverwacht in het 'team' en wat ik toen niet wist was dat ik je broodnodig had. Jij hielp me planningen maken, waar ik me vervolgens niet aan hield. Ik kon ook over privé omstandigheden mijn ei bij jou kwijt en het voelde vertrouwd en veilig. Bedankt voor het samen schrijven en sparren, de gezellige schrijf(mid)dagen en filmavonden (met pizza!). Zonder jou was ik nu nog steeds bezig met de inleiding van mijn eerste artikel.



# Chapter 1

## General introduction

# General introduction

Substance (ab)use has profound societal, psychological but also cognitive consequences, as many substances have a direct or indirect impact on the cognitive functioning of the brain. Characterizing these cognitive consequences is highly relevant for treatment of and care for individuals with a substance use disorder.

According to the latest available numbers of the National Alcohol and Drug Information System in the Netherlands (Wisselink et al., 2016), just short of 65,000 unique individuals were treated in addiction health care in 2015, with a declining trend since 2011. The most common primary substances of abuse are alcohol (45%), cannabis (17%), opioids (14%) and cocaine (11%). In about 42% of cases multiple substances are (ab)used (Wisselink et al., 2016). While the above numbers provide a clear image of the magnitude of the problem 'addiction', they most likely only reflect the tip of the iceberg as the substance users that do not seek treatment have not been taken into account. Of the patients who seek treatment, the prevalence of cognitive impairment is unclear.

In this introductory chapter of my thesis I will first discuss the concept of substance use disorder (SUD) and the terminology used in this field. I will then provide an overview of what kind of cognitive deficits may occur by briefly summarizing the evidence for the impact of different substances on cognitive functioning. Next, I will discuss the consequences that cognitive impairments have on treatment and its outcome. Subsequently, I will explain in more detail the challenges in the assessment of these impairments and the use of cognitive screeners. Finally, I will end this introduction with an outline of my thesis.

### *Substance–related and addictive disorders*

In the Diagnostic and Statistical Manual of Mental Disorders (DSM–5; American Psychiatric Association, 2013), the term 'addiction' is no longer being used. Instead, the new class 'Substance–related and Addictive Disorders' is used, which is divided into SUD and substance–induced disorders. The latter includes intoxication, withdrawal and other mental disorders that are induced by the substance. The former, SUD, is described as: 'a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance despite significant substance–related problems.' (APA, 2013, p. 483).

### *Substance–induced neurocognitive disorder*

What all substances have in common, is that they act directly on the reward system of the brain, which may result in brain changes that are sometimes irreversible (APA, 2013). Chronic substance (ab)use has acute and long–term effects on cognitive functioning. In the DSM–5 these effects are classified as either mild or major substance–induced Neurocognitive Disorders (NCD; APA, 2013), based on the severity of the cognitive decline from a previous level of performance. The cognitive sequelae can be present in various domains, including complex attention (e.g. sustained attention, divided attention, selective attention, processing speed), executive function (e.g. planning, decision making, working memory, error correction, inhibition, mental flexibility), learning and memory (e.g. working memory, short–term memory, long–term memory), language (e.g. expressive and receptive language, such as fluency, grammar and syntax), perceptual motor abilities (e.g. visual perception, visuo–construction, praxis, gnosis), and social cognition (e.g. recognition of emotions, theory of mind). As these effects vary per substance, both quantitatively and qualitatively, a brief summary of the evidence for the different substances is now provided.

*Alcohol*

In alcohol use disorder (AUD), it is estimated that about half of all patients seeking treatment have cognitive deficits (Rourke & Grant, 2009). In about 10% of cases these deficits are very severe, and also include for instance patients with Korsakoff's Syndrome (KS). The effects of alcohol on cognitive performance have been widely studied, possibly because it is the most widely used legal drug. Mild NCD may be the result of the direct effects of long–term alcohol abuse, like the toxic actions of alcohol itself or the consequences of alcohol withdrawal, but also by indirect effects of alcohol use, such as thiamine deficiency or liver cirrhosis. Acute alcohol intoxication primarily acts upon rather specific neuropsychological functions associated with the prefrontal cortex, such as planning, verbal fluency, memory and complex motor control, both in experimental (Peterson et al., 1990) and naturalistic settings (Lyvers & Tobias–Webb, 2010). On the contrary, the effects of alcohol on cognitive functioning post–detoxification are diffuse across 12 cognitive domains (Stavro et al., 2013). After one to three weeks of abstinence, chronic alcohol use is associated with decrements in memory, visuospatial abilities and inhibition (van Holst & Schilt, 2011). After six months of abstinence, the most enduring deficits have been reported in the domains of visuospatial ability and decision making (Fernández–Serrano et al., 2011). Although partial and sometimes full recovery occurs after abstinence, effects may endure at least up to one year after abstinence (van Holst et al., 2011; Stavro et al., 2013; Crowe et al., 2020). On the extreme end of the alcohol–induced NCD–spectrum lies KS: a neuropsychiatric disorder that is caused by thiamine deficiency and mostly associated with chronic alcohol use (Arts et al., 2017). Well–known symptoms of KS include severe memory deficits, confabulations, apathy, disorders of affect, social–cognitive problems and impaired insight into the illness (Arts et al., 2017; Rensen et al., 2017).

*Cannabis*

Cannabis has been used both for recreational and medical purposes, and the potential cognitive consequences have been summarized recently (Le Foll & Tyndale, 2015). Currently, cannabis is considered the most frequently used illicit drug worldwide (Pope Jr et al., 2001). The acute consequences of intoxication primarily act upon the short–term memory, executive functioning and attention (Lundqvist, 2005). The long–term effects have been topic of much debate (Pope Jr et al., 2001). The effects would be noticeable after 17 hours (Solowij et al., 2002), seven days (Pope Jr et al., 2001) and even after 21 days of abstinence in the executive functioning domain (Crean et al., 2011), but the long term post–acute effects (more than 28 days) are assumed to be largely reversible (Pope Jr et al., 2001; van Holst et al., 2011). Indeed, a meta–analysis by Grant et al. (2003) showed that the effect sizes of the non–acute effects are zero for the majority of the cognitive domains. Only on general intelligence it was found that after 20 years of abstinence, users performed worse than non–users. However, after careful examination of the results, it appeared that this was only on one subtest of this domain, and a trend was present of users performing actually better than non–users on several other subtests. It was therefore concluded that long–term cognitive consequences of cannabis use are negligible (Lyons et al., 2004). Likewise, Schulte et al. (2014) mentioned that it is the only drug of which full recovery is possible, and Fernández–Serrano et al. (2011) concluded in their review that long–term effects are absent.

*Stimulants*

Concerning stimulant abuse, cocaine and methamphetamine have been of particular interest as they are widely used. For cocaine use, the cognitive deficits are considered to be relatively mild (Goldstein et al., 2004). Interestingly, the literature suggests that psychostimulants produce both cognitive enhancement and impairment. It is proposed that dose is the critical determinant herein, following an inverted U–shape when related to performance (Wood et al., 2014). Alternatively, it is argued that the effects of cocaine during acute intoxication and during abstinence seem to oppose each other, being generally advantageous and detrimental for cognitive functioning, respectively (Spronk et al., 2013). The acute effects of both cocaine and methamphetamine are highly similar, with cocaine use being associated with improved response inhibition, speed and psychomotor performance (Spronk et al., 2013), and methamphetamine use being associated with increased processing speed and alertness, although selective attention diminishes (Scott et al., 2007). In the acute stages of cocaine abstinence, decision making abilities may be negatively affected (Tucker et al., 2004). Cunha et al. (2004) have reported evidence for impairments in attention, memory, learning ability, and executive functions in chronic cocaine abusers after two weeks of abstinence. Regarding the effects during prolonged abstinence, both cocaine and methamphetamine abusers show decrements in executive functioning, inhibition, (verbal) memory and psychomotor functions (Scott et al., 2007; van Holst et al., 2011; Spronk et al., 2013). Jovanovski et al. (2005) conducted a

meta–analysis and concluded that in cocaine use disorder the largest effect size was found for attention and moderate effect sizes for memory. Longitudinal research suggests that at least partial recovery is possible after abstinence: Zhong et al. (2016) showed improvements in most cognitive domains in methamphetamine users after six months of abstinence. After one year of complete abstinence, cognitive functioning was found to be undistinguishable from non–using controls, both for cocaine users (Vonmoos et al., 2014) and methamphetamine users (Iudicello et al., 2010). Remarkably, a short period of abstinence of cocaine use is associated with less neuropsychological deficits than a longer period. A possible explanation is that recent cocaine use may mask possible deficits (Woicik et al., 2009; Schulte et al., 2014).

*Opioids*

Regarding opiate use, which includes substances like opium, heroin, codeine and morphine, relatively few studies have assessed the acute effects of substance intake. In their review, Gruber et al. (2007) describe evidence for impairments in the memory domain. More recently, Kroll et al. (2018) found that opioid users were significantly impaired as compared to non–users in the domains attention, declarative memory and global cognitive empathy, for which a negative dose–dependent correlation was found. The effects during abstinence are deficits in executive functioning, such as verbal fluency, inhibition and decision–making skills, and these effects exist up to one year of abstinence (van Holst et al., 2011). Whether recovery occurs is largely unknown, although it appears that substitution therapy, in which the drug of abuse is replaced with methadone, is actually linked to cognitive decline itself (Davis et al., 2002; van Holst et al., 2011). Davis et al. (2002) concluded that at least some recovery is possible after abstinence.

*Gamma–hydroxybutyrate*

Gamma–hydroxybutyrate (GHB) is a central nervous system depressant drug that has been introduced in the late nineties. It is an odourless and colourless liquid, with a soapy or salty taste, it is often combined with alcohol and is also known as a ‘date rape’ drug. In the limited amount of research on the cognitive consequences of GHB, there are several studies that suggest negative effects. For instance, a double blind, placebo controlled study in healthy participants showed that GHB intoxication temporarily impaired working and episodic memory, in a dose dependent manner (Carter et al., 2009). It was recently studied that GHB–induced comas are associated with (verbal) memory impairments (Raposo Pereira et al., 2018a; Raposo Pereira et al., 2018b) and alterations in long–term memory networks and lower hippocampus/lingual gyrus activity while performing memory tasks (Raposo Pereira et al., 2018b).

***Consequences of neurocognitive disorders for treatment***

The presence of substance–induced NCD affects the course and results of addiction treatment. For instance, having NCD predicts higher drop–out rates during treatment (Teichner et al., 2002), and decreases the likelihood of attending all therapy sessions (Copersino et al., 2012). Treatment results are worse for patients with NCD than for those without, including lower treatment retention and less reported abstinence (Aharonovich et al., 2003; Aharonovich et al., 2006). Also, patients with NCD may not recognize their problematic substance use and show less intention to stop using (Severtson et al., 2010). Also, they have lower self–efficacy, which is in turn predictive of less abstinent days and larger amounts of use on a using day (Bates et al., 2006). Finally, patients with substance–induced NCD show higher relapse rates (Dijkstra et al., 2017). If SUD treatment takes NCD into account, this may lead to improvement of cognitive functioning (Forsberg & Goldman, 1987; Roehrich & Goldman, 1993; Sofuoglu et al., 2010). Therefore, the consequences of having NCD and entering 'regular' addiction treatment, show the need to diagnose early.

***Assessment of neurocognitive disorders: evidence and challenges***

Although we can assume that NCD occurs in a large number of patients with SUD, it is often a challenge to identify in clinical practice patients who actually have NCD. For instance, self–report measures of cognitive function are feasible in this group, but do not provide a valid estimate of the patients' cognitive status, as patients are not always aware of their cognitive deficits. This is also illustrated by a lack of correlation between objectively measured and subjectively experienced cognitive deficits (Horner et al., 1999). More recently, Walvoort et al. (2016) also found that a higher degree of illness insight is associated with better cognitive functioning. An important finding, as this implies that even clinicians are not aware of patients having cognitive deficits without neuropsychological test results backing up the observations. This demonstrates the importance of properly diagnosing substance–induced NCD based on a standardized neuropsychological assessment (NPA).

*Neuropsychological assessment*

Administration of an NPA has several drawbacks. It is time consuming, relatively expensive, not always available and it requires highly experienced clinicians and patients who are motivated to participate in an NPA. This motivation is even more tested when a period of abstinence is first needed. For instance, patients should be able to remain abstinent for a minimal period of six weeks to minimize the intoxicating effects of alcohol in the brain (Walvoort et al., 2013). Therefore, administering an NPA to all patients entering addiction treatment is not feasible.

This gap between knowledge – exactly knowing what needs to be done to plan well indicated treatment – and clinical reality – realizing an NPA for each individual is impossible – may be closed by administering a brief cognitive screener, which can give a quick indication of the current cognitive status. An ideal screening instrument should meet certain criteria (Shulman, 2000). For instance, it should have a short administration time and have an easy to interpret score, it should be relatively independent of education, language or culture, have good psychometric properties such as test–retest and inter–rater reliability, and good concurrent and predictive validity with high levels of sensitivity and specificity. Above all, it must be easy to score and be acceptable in administration for both the clinician and the patient. Ideally, a cognitive screener should have parallel versions that enable longitudinal assessment in individual patients while minimizing material–specific practice–effects.

There are many different cognitive screening instruments available, not all meeting the abovementioned criteria. Probably the best known and most widely used is the Mini Mental State Examination (MMSE; Folstein et al., 1975). A limitation of the MMSE is its low sensitivity in detecting mild NCD. Other well–known cognitive screening instruments are the Mini–Cog (Borson et al., 2000) and Addenbrooke's Cognitive Examination Revised (ACE–R; Mioshi et al., 2006). These instruments have, however, been developed for the assessment of severe cognitive disorders (such as dementia) and not for use in addiction health care, and they may not be universally available.

*Montreal Cognitive Assessment*

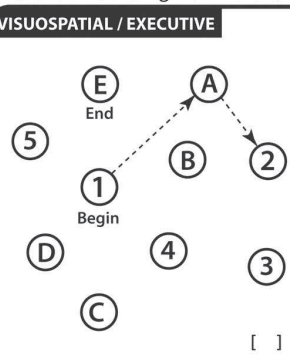
A potentially promising cognitive screening instrument for detecting substance–induced neurocognitive disorders is the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; see www.mocatest.org). The MoCA was initially developed to detect mild NCD due to Alzheimer's Disease and contains 12 items in seven cognitive domains. It is a brief test with a scoring range from 0 to 30. Administration of the instrument takes about ten to fifteen minutes and there are three alternate versions available, making it possible to retest over time. The MoCA has been used as a cognitive screener in many populations, such as, but not limited to, cerebrovascular disorders, Parkinson's disease, HIV, head trauma, sleep behaviour disorders, brain tumours, depression, heart failure, and also substance use disorders. It is freely available in about 60 languages in 40 countries.

In 2010, the Dutch version of the MoCA (version 7.1, see Figure 1.1) was made available and validated in a memory clinic population (Thissen et al., 2010). For the purpose of the current PhD project authorized translations of versions 7.2 and 7.3 were made (Wester & Kessels, 2012).

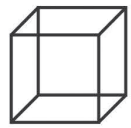
**MONTREAL COGNITIVE ASSESSMENT (MOCA)**
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

**VISUOSPATIAL / EXECUTIVE** — POINTS

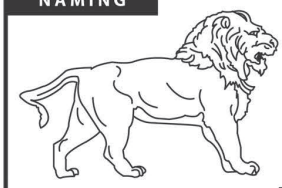



Copy cube [ ]



Draw CLOCK (Ten past eleven) ( 3 points ) [ ] Contour [ ] Numbers [ ] Hands __/5

**NAMING**



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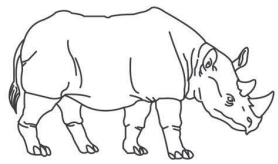

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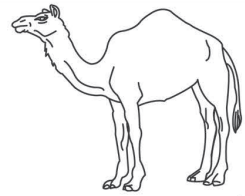

[ ] __/3

**MEMORY** Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | | | | | |
| 2nd trial | | | | | |

No points

**ATTENTION** Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

**LANGUAGE** Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

**ABSTRACTION** Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

**DELAYED RECALL**

| | Has to recall words WITH NO CUE | FACE | VELVET | CHURCH | DAISY | RED | Points for UNCUED recall only |
|---|---|---|---|---|---|---|---|
| | | [ ] | [ ] | [ ] | [ ] | [ ] | |
| **Optional** | Category cue | | | | | | |
| | Multiple choice cue | | | | | | |

__/5

**ORIENTATION** [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

***Figure 1.1.*** Montreal Cognitive Assessment – Version 7.1, Original Version; copyright Z. Nasreddine MD. Reproduced with permission. It is mandatory to follow the online MoCA© Training and Certification Program to administer and score the MoCA©. Copies are available at www.mocatest.org.

***Outline of this thesis***

The primary aim of this thesis is to investigate cognitive impairments in patients with SUD and whether the MoCA is a reliable and valid cognitive screening instrument to detect these, to overcome the aforementioned challenges that come with an extensive NPA. The secondary aim is to investigate if and how the MoCA can be further implemented in addiction health care.

In Chapter 2, the psychometric properties of all three Dutch versions of the MoCA will be investigated in a large sample of healthy participants from a wide age range. In addition, the effect of age, sex and (estimated premorbid) intelligence are examined.

Questions that will be answered:

- Are demographic variables age, sex, educational level and estimated premorbid intelligence associated with performance on the MoCA?
- Are the parallel versions of the MoCA equivalent?
- What is the test–retest reliability between versions of the MoCA?

In Chapter 3, the validity and applicability of the MoCA will be investigated for use in addiction health care, aiming to provide an optimal cut–off based on an extended NPA. Also, the effect of substance type and abstinence duration on MoCA performance will be examined here.

Questions that will be answered:

- Can an optimal cut–off score of the MoCA be determined for use in addiction health care?
- What is the criterion validity (both predictive and concurrent) of the MoCA as compared to an extensive NPA?
- Does substance type and/or abstinence duration affect performance on the MoCA?

In Chapter 4, the MoCA will be used to estimate the prevalence of NCD in addiction health care, while taking important patient characteristics into account (i.e. age, years of regular use, polysubstance use, severity of dependence/abuse, depression, anxiety and stress).

Questions that will be answered:

- What is, at intake, the prevalence of cognitive impairments in patients using different substances?
- Are there differences in cognitive performance across substances per cognitive domain?
- What are the effects of age, abstinence, abstinence duration, polysubstance use, duration of regular use, severity of dependence/abuse, depression, anxiety and stress on cognitive functioning in SUD.

Chapter 5 will provide a closer look at the course of cognitive performance and everyday cognitive functioning in patients with alcohol use disorder with or without NCD.

Questions that will be answered:

- What is the course of cognitive performance on the MoCA during treatment towards abstinence and recovery in three patient groups with AUD: patients with AUD without cognitive impairments, patients with alcohol–related cognitive impairments (ARCI), and patients with KS?
- What is the course of everyday cognitive functioning in these three patient groups, as measured with the Patient Competency Rating Scale (PCRS)?
- Are changes in cognitive performance (MoCA) related to changes in everyday cognitive functioning (PCRS) between the sixth week of admission and clinical discharge?

In Chapter 6, the MoCA will be used to examine if cognitive impairments predict relapse in patients with GHB use disorder.

Questions that will be answered:

- What is the association between cognitive impairment, the number of GHB–induced comas and severity of GHB use?
- What is the association between cognitive impairment and relapse in GHB use after detoxification?

Finally, in Chapter 7 the findings of my thesis will be summarized and discussed and a perspective for clinical practice and future research will be provided.

Alle oud–collega's van het Korsakov Centrum, met het risico dat ik belangrijke mensen vergeet ga ik toch enkele namen noemen: Henny en Karin, voor het heerlijke kletsen voor, tijdens en na de koffiepauze. Kelly en Renée, collega's van mijn eerste uur, bedankt dat jullie mij wegwijs hebben gemaakt in de neuropsychologische testdiagnostiek. Kelly, het waren super gezellige carpool–ritjes die ik nooit zal vergeten.

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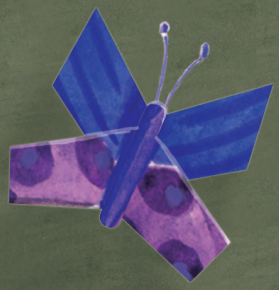

# Chapter 2

## Psychometric properties of the Montreal Cognitive Assessment (MoCA) in healthy participants aged 18–70

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## Abstract

The Montreal Cognitive Assessment (MoCA) is a cognitive screen, available in three alternate versions. The aims of the current study were to examine the effects of age, education and intelligence on MoCA performance and to determine the alternate–form equivalence and test–retest reliability of the MoCA, in a group of healthy participants. In 210 participants, two MoCA versions and an estimator for premorbid intelligence were administered at two time points. Age, education and estimated premorbid intelligence correlated significantly with the MoCA Total Score (MoCA–TS) and the Memory Index Score (MoCA–MIS). Systematic differences between MoCA version 7.1 and alternate versions 7.2 and 7.3 were only found for the items animal naming, abstract reasoning and sentence repetition. Test–retest reliability of the MoCA–TS was good between 7.1 and 7.2 (ICC = 0.64) and excellent between 7.1 and 7.3 (ICC = 0.82). For the MoCA–MIS, coefficients were poor (ICC = 0.32) to fair (ICC = 0.48), respectively. Adequate norms are needed that take the effects of age, education and intelligence on MoCA performance into account. All three MoCA versions are largely equivalent based on MoCA–TS and the test–retest reliabilities show that this score is suitable to monitor cognitive change over time. Comparisons of the domain–specific scores should be interpreted with caution.

# Introduction

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is one of many available cognitive screening instruments. The screener contains 12 items measuring seven cognitive domains: executive functioning; visuospatial abilities; language; attention, concentration and working memory; abstract reasoning; memory and orientation. Recently, the Memory Index Score (MoCA–MIS) was developed as an additional clinical outcome measure to assess the severity of memory impairments (Julayanont et al., 2014). The MoCA was developed to be more sensitive to mild cognitive impairment in geriatric populations than other screeners, like the Mini Mental State Examination (MMSE; Folstein et al., 1975), and has been translated into nearly 100 languages. Besides geriatrics, the MoCA is widely used in, for instance, substance use, HIV and hepatitis C (Copersino et al., 2009; Bassiony et al., 2015; Janssen et al., 2015; Bruijnen et al., 2016). Although the MoCA has gained wide support, research focussing on its psychometric properties, such as alternate–form–, test–retest– and inter–rater reliability, has yielded mixed findings. Moreover, the influence of educational attainment, age and sex on the test performance has been under debate. A short overview of these mixed findings is discussed below (see also Julayanont et al., 2013).

With respect to educational attainment, Nasreddine et al. (2005) found that years of education affect MoCA performance. As a result, they suggested to add one 'correction point' to scores of individuals with 12 years of education or less. Bruijnen, Jansen, et al. (2019) recently proposed a more fine–grained correction method based on the level of education, rather than its duration, where individuals with a low level of education receive two additional points and those with an average level of education receive one additional point. Only one study correlated MoCA scores with general intellectual abilities and found a correlation of 0.64 (Sugarman & Axelrod, 2014). With respect to age, (Nasreddine et al., 2005) in their study in healthy adults between 55 and 85, did not find this characteristic to be of influence on MoCA performance. However, recent studies have demonstrated a negative correlation between age and MoCA scores in a slightly wider age range of 50–100 years (Malek–Ahmadi et al., 2015; Oren et al., 2015; Yancar Demir & Özcan, 2015; Apolinario et al., 2018). Also, an interaction effect between age and education was found, in which younger participants with higher education levels had higher MoCA scores, compared to older participants with lower education levels (Zheng et al., 2012). Normative data correcting for age, education and sex have been presented for several translations (Larouche et al., 2016; Ojeda et al., 2016; Borland et al., 2017; Thomann et al., 2018), while others found no effect of sex on MoCA performance (Zheng et al., 2012; Santangelo et al., 2015; Kopecek, Stepankova, et al., 2017; Apolinario et al., 2018). Although there are some studies presenting normative data, these are currently not as widely used as the aforementioned correction method by Nasreddine et al. (2005).

With respect to alternate–form reliability, relevant for repeated assessment in individuals with the aim to overcome material–specific learning effects, Chertkow et al. (2011) developed two alternate versions of the original version (MoCA alternate versions 7.2 and 7.3). The alternate versions have been translated into nearly 40 languages, including Dutch. The MoCA Total Score (MoCA–TS) of the English, French and several other translations was found to be systematically equivalent across versions (Chertkow et al., 2011; Nasreddine & Patel, 2016). However, looking at item level one study in geriatric patients showed systematic differences between the original and both alternate versions for the items figure copy, animal naming and abstract reasoning (Lebedeva et al., 2016), but studies in healthy individuals are lacking.

Finally, the test–retest and inter–rater reliability are important for repeated assessments. The test–retest reliability of the English–language versions, and the German and Czech translations of MoCA 7.1 and 7.2 range from 0.42 to 0.81, for MoCA–TS (Costa et al., 2012; Feeney et al., 2016; Kopecek, Bezdicek, et al., 2017; Wu et al., 2017). The lowest reliability was found after an administration interval of three years (Kopecek, Bezdicek, et al., 2017). The inter–rater reliability of the items alternating trail making, figure copy and clock drawing of MoCA version 7.1 was recently investigated in a large multicentre trial, including 1119 participants (Cumming et al., 2020). Kappa coefficients ranging from 0.46 (hands of the clock) to 0.94 (alternating trail making) were found, where a higher coefficient means better agreement between raters.

As can be seen from this overview, differences in MoCA properties exist between populations and translations, and mixed results have been found for participants with different sociodemographic characteristics. As the MoCA is increasingly being administered to individuals younger than 50, it is important to determine the psychometric properties of the Dutch translations of the MoCA in a wide age range. The aims of the current study are, therefore, to assess psychometric properties of the MoCA in healthy participants. We will investigate: 1) whether demographic variables such as age, sex, educational level and estimated premorbid intelligence are associated with performance on the MoCA; 2) whether systematic differences between MoCA version 7.1 and alternate versions 7.2 or 7.3 can be found and 3) what the test–retest reliability between MoCA version 7.1, and alternate versions 7.2 and 7.3 is.

# Methods

### Design

A repeated–measures within–subject design was used in which MoCA version 7.1 and one of the alternate versions 7.2 or 7.3 were administered, with an interval of two to four weeks. Data were collected between March 2012 and December 2016, as part of a larger research project on the applicability of the MoCA in addiction care.

### Participants

The main inclusion criterion was an age between 18 and 70. Exclusion criteria were: 1) a current diagnosis of substance or behavioural abuse/dependence according to DSM–5 (APA, 2013) criteria, excluding nicotine; 2) self–reported presence or history of neurological disorders (e.g. stroke, dementia, traumatic brain injury, Korsakoff's syndrome); 3) self–reported presence or history of an otherwise defined psychotic, psychiatric and/or medical condition that, in the view of this study, would interfere with administration of the MoCA and/or otherwise compromise participation. In total, 218 healthy participants were recruited, one of whom was excluded from further analyses for not meeting the inclusion criterion (i.e. aged 17). Of the remaining 217 participants, seven had completed MoCA version 7.2 and 7.3, and not MoCA version 7.1. As this group was too small to make reliable comparisons between these two alternate versions, these participants were also excluded. Participants were recruited via the personal network of the assessors, by contacting companies and associations, via mouth to mouth, or via social media.

### Materials

*Montreal Cognitive Assessment*

The authorised Dutch translations of three alternate versions of the MoCA were used in this study. MoCA version 7.1 was translated in 2010 by Dautzenberg and De Jonghe (Thissen et al., 2010) and MoCA alternate versions 7.2 and 7.3 were translated in 2012 by Wester and Kessels. The MoCA consists of 12 items: alternating trail making (0–1 point), figure copy (0–1 point), clock drawing (0–3 points), animal naming (0–3 points), digit span (0–2 points), sustained attention (0–1 point), serial subtraction (0–3 points), sentence repetition (0–2 points), verbal fluency (0–1 point), abstract reasoning (0–2 points), memory (delayed recall, 0–5 points) and orientation (0–6 points).

All items add up to MoCA–TS, with a maximum of 30 points, where a higher score represents better cognitive functioning. In this study, the unadjusted raw MoCA–TS was used in all analyses (i.e. not adding points for individuals with lower educational levels). Seven Domain Scores (MoCA–DS) were calculated: executive functioning (alternating trail making and verbal fluency: 0–2 points), visuospatial abilities (figure copy and clock drawing: 0–4 points), attention,

concentration and working memory (digit span, sustained attention and serial subtraction: 0–6 points), language (animal naming and sentence repetition: 0–5 points), abstract reasoning (0–2 points), memory (0–5 points) and orientation (0–6 points). Finally, the MoCA–MIS was calculated, in which freely recalled words receive three points, words recalled after a category cue receive two points (cued recall) and correct identification after a multiple–choice cue (recognition) receives one point, with a maximum of 15 points (Julayanont et al., 2014).

The first author thoroughly checked all scores and corrected scoring errors when needed. This check revealed ambiguities in the scoring, mainly for the item figure copy, for which the scoring instructions were not fully specified. Therefore, all figures were scored in a consistent manner according to strict criteria by the first author. This procedure also eliminated inter–rater differences that were found to influence results (Cumming et al., 2020).

*National Adult Reading Test*

The Dutch version of the National Adult Reading Test (NART; Nelson, 1982), an important tool for estimating premorbid levels of intelligence (Bright et al., 2018), was administered. The test consists of 50 words with an uncommon pronunciation. The participant is instructed to read these words aloud in the correct pronunciation. Each answer is awarded 0–2 points, where 0 = false, 1 = questionable, 2 = correct pronunciation, with a maximum of 100 points. Norm scores based on age and sex are added to the total score to determine the estimated premorbid intelligence (NART–IQ; Schmand et al., 1992).

***Procedure***

MoCA and NART administration and scoring were performed by four assessors with a background in psychology who received extensive training by the first author. With respect to ethical clearance, the study design was approved by the ethics review committee of the Faculty of Social Sciences of Radboud University and the Institutional Review Board of Vincent van Gogh Institute for Psychiatry. After written informed consent was obtained, an appointment was made for the administration of the tasks. Relevant demographic data were recorded via a self–report questionnaire. Level of education was classified on a seven–point scale ranging from 1 = less than primary school to 7 = a university master's degree or higher (Duits & Kessels, 2014), based on the Dutch educational system. This is a classification system that is comparable to the International Standard Classification of Education (ISCED; United Nations Educational Scientific and Cultural Organization, 2012). Next, the NART was administered followed by one of the MoCA versions. A second appointment was then made in which another version of the MoCA was administered. Assessments took place in a quiet room at the office or at the participant's home for logistic reasons, that is, to reduce recruitment bias, make flexible appointments possible, and to reduce travel time for participants.

Data sets from three smaller studies were combined. In the first study, the NART and MoCA version 7.1 were administered in 34 participants. In the second study, MoCA version 7.1 and 7.2 were administered in this fixed order in 74 participants. In the third study, 103 participants completed the NART, and two versions of the MoCA were administered in a counterbalanced order: MoCA version 7.1 and 7.2 (51 participants), and MoCA version 7.1 and 7.3 (52 participants).

***Analyses***

*Participant characteristics and Montreal Cognitive Assessment scores*

The participant characteristics for age, age category (for which age was categorised into two groups, i.e. 18–54 and 55–70 years), sex, educational level and estimated premorbid intelligence are presented for the total sample. Next, a description of MoCA scores on all items, and the mean MoCA–TS, –DS and –MIS were provided for each version.

*Demographic factors*

In the analyses examining the influence of demographic factors on MoCA performance, only participants were included in whom MoCA version 7.1 was administered first, eliminating possible learning effects. The influence of age, educational level and estimated premorbid intelligence on MoCA–TS and –MIS were determined using Pearson's correlations or Spearman's rho (if assumptions of normality were not met). The influence of sex and age category on MoCA–TS was determined using independent *t*–tests and to determine the influence of these variables on MoCA–MIS, Mann–Whitney tests were used.

*Systematic differences*

The equivalence of the MoCA versions was determined by using all participants in whom MoCA 7.1 and one of the alternate versions were administered in a counterbalanced order, to reduce the chances of the order of administration adversely influencing the results. Equivalence was determined for the MoCA–TS, –DS, –MIS and for each item by examining possible systematic differences using Wilcoxon signed–rank two–related–samples tests or McNemar's test (for all dichotomous scores).

*Test–retest reliability*

The test–retest reliability was determined using all participants in whom administration of MoCA 7.1 was followed by one of the alternate versions. By using two–way mixed intra–class correlations (ICC) with absolute agreement, the test–retest reliability for the MoCA–TS, –DS, –MIS and each item was determined. An ICC of less than 0.40 is indicative of poor reliability, between 0.40 and 0.59 is considered fair, between 0.60 and 0.74 good, and an ICC of 0.75 and above indicates excellent reliability (Cicchetti, 1994). All data were computed and analysed with IBM SPSS version 25.0.

# Results

### *Participant characteristics and Montreal Cognitive Assessment scores*

Table 2.1 provides an overview of participant characteristics for the total sample. Table 2.2 presents an overview of the mean MoCA–TS, –DS and –MIS, and a frequency distribution of all item scores, for all three versions.

***Table 2.1.*** Participant characteristics, frequency of administration and administration interval of the Montreal Cognitive Assessment (MoCA), for the total sample.

| | Total sample (*n* = 210) |
|---|---|
| Mean age in years (*SD*) | 35.3 (16.4) |
| 18 – 54 years (%) | 170 (81.0) |
| 55 – 70 years (%) | 40 (19.0) |
| Sex (%) | |
| male | 78 (37.1) |
| female | 132 (62.9) |
| Level of education (%) | |
| 2: primary school | 1 (0.5) |
| 3: more than primary school, no other diploma's | 6 (2.9) |
| 4: lower secondary education | 16 (7.6) |
| 5: average secondary education | 120 (57.1) |
| 6: higher secondary education/a university bachelor's degree | 55 (26.2) |
| 7: a university master's degree/a post–doc degree | 12 (5.7) |
| NART–IQ (%; *n* = 121) | 98.1 (11.6) |
| range | 67 – 135 |
| MoCA administration (%) | |
| 7.1 | 44 (21.0) |
| 7.1 – 7.2 | 84 (40.0) |
| 7.2 – 7.1 | 27 (12.9) |
| 7.1 – 7.3 | 29 (13.8) |
| 7.3 – 7.1 | 26 (12.4) |
| Mean administration interval in days (*SD*; *n* = 166) | 22.1 (10.1) |
| range | 5 – 65 |

Note: *SD* = standard deviation; NART–IQ = National Adult Reading Test – estimated premorbid intelligence.

***Table 2.2.*** Means and standard deviations (*SD*) for the Montreal Cognitive Assessment (MoCA) total (MoCA–TS), domain (MoCA–DS) and memory index scores (MoCA–MIS), and frequency distribution of scores per item, for each version in the total sample.

| | MoCA 7.1 | MoCA 7.2 | MoCA 7.3 |
|---|---|---|---|
| | (*n* = 210) | (*n* = 111) | (*n* = 55) |
| Mean MoCA–TS | 25.50 (2.27) | 25.13 (2.67) | 26.16 (1.96) |
| scoring range (0 – 30) | 19 – 30 | 15 – 30 | 21 – 30 |
| Mean MoCA–DS | | | |
| executive functioning | 1.50 (0.61) | 1.67 (0.49) | 1.67 (0.47) |
| visuospatial abilities | 2.88 (0.89) | 2.84 (0.78) | 2.85 (0.97) |
| attention | 5.70 (0.55) | 5.55 (0.78) | 5.76 (0.47) |
| language | 4.48 (0.67) | 4.17 (0.84) | 4.04 (0.58) |
| abstract reasoning | 1.45 (0.56) | 1.61 (0.62) | 1.91 (0.29) |
| memory | 3.63 (1.13) | 3.36 (1.31) | 4.07 (1.14) |
| orientation | 5.86 (0.36) | 5.93 (0.26) | 5.85 (0.36) |
| | (*n* = 159) | (*n* = 65) | (*n* = 55) |
| Mean MoCA–MIS | 13.15 (1.80) | 13.57 (1.08) | 13.76 (1.48) |
| scoring range (0 – 15) | 6 – 15 | 11 – 15 | 9 – 15 |
| Item score frequency distribution | (*n* = 210) | (*n* = 111) | (*n* = 55) |
| alternating trail making (0/1) | 29/181 | 10/101 | 3/52 |
| copy figure (0/1) | 135/75 | 87/24 | 33/22 |
| clock drawing (0/1/2/3) | 0/16/68/126 | 0/6/30/75 | 0/7/16/32 |
| naming (0/1/2/3) | 0/1/24/185 | 0/0/17/94 | 0/0/1/54 |
| digit span (0/1/2) | 1/25/184 | 2/27/82 | 0/6/49 |
| sustained attention (0/1) | 6/204 | 4/107 | 1/54 |
| serial subtraction (0/1/2/3) | 0/5/20/185 | 0/5/5/101 | 0/1/4/50 |
| sentence repetition (0/1/2) | 7/69/134 | 15/45/51 | 7/38/10 |
| verbal fluency (0/1) | 77/133 | 27/84 | 15/40 |
| abstract reasoning (0/1/2) | 7/101/102 | 8/27/76 | 0/5/50 |
| memory (0/1/2/3/4/5) | 3/5/22/61/64/55 | 4/7/14/28/36/22 | 0/2/5/6/16/26 |
| orientation (0/1/2/3/4/5/6) | 0/0/0/0/1/28/181 | 0/0/0/0/0/8/103 | 0/0/0/0/0/8/47 |

***Demographic factors***

MoCA–TS was negatively related to age ($\rho$ = −0.21, $p$ = .009) and age category ($t(155)$ = 3.63, $p$ < .001), and positively correlated with level of education ($\rho$ = 0.47, $p$ < .001) and estimated premorbid intelligence ($r$ = 0.51, $p \leq .001$). Sex was not related to MoCA–TS ($t(155)$ = 0.59, $p$ = .557).

MoCA–MIS was negatively related to age ($\rho$ = −0.26, $p$ = .003) and age category ($U$ = 255.50, $z$ = −3.96, $p$ < .001, $r$ = −0.35). Younger participants (*Mdn* = 14.00) scored significantly higher (and near–ceiling) than older participants (*Mdn* = 11.00). A positive correlation was found between MoCA–MIS and level of education ($\rho$ = 0.32, $p$ < .001), and estimated premorbid intelligence ($\rho$ = 0.34, $p$ = .016). With respect to sex, men (*Mdn* = 13.00) scored significantly lower than women (*Mdn* = 14.00; $U$ = 1520.50, $z$ = −2.14, $p$ = .032, $r$ = −0.19).

***Systematic differences***

Systematic differences were found across alternate versions for the items animal naming, sentence repetition and abstract reasoning. For animal naming, scores on version 7.1 were lower than on version 7.3 ($T$ = 1, $z$ = −2.53, $p$ = .011, $r$ = −0.34). For sentence repetition, scores on version 7.1 were higher than those on both version 7.2 ($T$ = 10, $z$ = −2.52, $p$ = .012, $r$ = −0.34) and version 7.3 ($T$ = 3, $z$ = −5.09, $p$ < .001, $r$ = −0.69). Both animal naming and sentence repetition are part of the language domain, for which scores on version 7.1 were found to be significantly higher than on both version 7.2 ($T$ = 9, $z$ = −2.59, $p$ = .010, $r$ = −0.35) and version 7.3 ($T$ = 6, $z$ = −3.74, $p$ < .001, $r$ = −0.50). As for the item abstract reasoning, which is also a MoCA–DS, scores on version 7.1 were lower than those on both version 7.2 ($T$ = 6, $z$ = −2.69, $p$ = .007, $r$ = −0.36) and version 7.3 ($T$ = 4, $z$ = −2.56, $p$ = .011, $r$ = −0.34). MoCA–TS, –MIS and the other MoCA–DS and items, did not differ between versions.

***Test–retest reliability***

Tables 2.3 and 2.4 show the ICCs with means and standard deviations for the MoCA–TS, –DS and –MIS, and for all items, between versions 7.1–7.2 and 7.1–7.3, respectively. The test–retest reliability for both MoCA–TS and –MIS was higher between version 7.1–7.3 (MoCA–TS: ICC = 0.82; MoCA–MIS: ICC = 0.48), than between version 7.1–7.2 (MoCA–TS: ICC = 0.64; MoCA–MIS: ICC = 0.32). For MoCA–DS of version 7.1–7.2, the ICCs ranged from poor (0.18 for language) to good (0.60 for visuospatial abilities). For version 7.1–7.3, the ICCs ranged from poor (0.38 for attention, concentration and working memory) to fair (0.57 for memory), excluding two negative ICCs (abstract reasoning, −0.29 and orientation, −0.32).

***Table 2.3.*** Means and standard deviations (*SD*) for the Montreal Cognitive Assessment (MoCA) total (MoCA-TS), domain (MoCA-DS), memory index (MoCA-MIS) and item scores for both version 7.1 and alternate version 7.2, and test–retest reliability (intraclass–correlation; ICC) between versions.

| | MoCA 7.1 | MoCA 7.2 | ICC | 95% CI | *p*–value |
|---|---|---|---|---|---|
| | ($n$ = 84) | | | | |
| Mean MoCA–TS | 25.10 (2.15) | 25.58 (2.28) | 0.64 | 0.44–0.76 | < 0.001 |
| Mean MoCA–DS | | | | | |
| executive functioning | 1.44 (0.63) | 1.70 (0.49) | 0.44 | 0.14–0.63 | 0.002 |
| visuospatial abilities | 2.85 (0.87) | 2.99 (0.69) | 0.60 | 0.38–0.74 | < 0.001 |
| attention | 5.52 (0.69) | 5.51 (0.83) | 0.49 | 0.21–0.67 | 0.001 |
| language | 4.38 (0.68) | 4.19 (0.86) | 0.18 | −0.26–0.46 | 0.183 |
| abstract reasoning | 1.49 (0.55) | 1.68 (0.58) | 0.31 | −0.04–0.55 | 0.037 |
| memory | 3.49 (1.04) | 3.56 (1.19) | 0.30 | −0.08–0.55 | 0.054 |
| orientation | 5.93 (0.26) | 5.95 (0.21) | 0.54 | 0.29–0.70 | < 0.001 |
| | ($n$ = 60) | | | | |
| Mean MoCA–MIS | 13.20 (1.48) | 13.67 (1.00) | 0.32 | −0.10–0.59 | 0.060 |
| Mean item scores[a] | | | | | |
| alternating trail making | 0.82 (0.39) | 0.92 (0.28) | 0.56 | 0.32–0.71 | < 0.001 |
| copy figure | 0.29 (0.45) | 0.24 (0.43) | 0.34 | −0.02–0.57 | 0.031 |
| clock drawing | 2.56 (0.63) | 2.75 (0.46) | 0.45 | 0.17–0.64 | 0.002 |
| animal naming | 2.88 (0.36) | 2.83 (0.38) | −0.35 | −1.09–0.13 | 0.912 |
| digit span | 1.80 (0.43) | 1.71 (0.48) | 0.22 | −0.20–0.49 | 0.130 |
| sustained attention | 0.98 (0.15) | 0.95 (0.21) | 0.48 | 0.20–0.66 | 0.002 |
| serial subtraction | 2.75 (0.54) | 2.85 (0.50) | 0.41 | 0.09–0.61 | 0.009 |
| sentence repetition | 1.50 (0.55) | 1.36 (0.71) | 0.34 | −0.00–0.57 | 0.026 |
| verbal fluency | 0.62 (0.49) | 0.79 (0.41) | 0.45 | 0.16–0.64 | 0.002 |

Note: [a] = item scores for abstract reasoning, memory and orientation are not shown, as they are the same as the domain scores.

***Table 2.4.*** Means and standard deviations (*SD*) for the Montreal Cognitive Assessment (MoCA) total (MoCA-TS), domain (MoCA-DS), memory index (MoCA-MIS) and item scores for both version 7.1 and alternate version 7.3, and test–retest reliability (intraclass–correlation; ICC) between versions.

| | MoCA 7.1 | MoCA 7.3 | ICC | 95% CI | *p*–value |
|---|---|---|---|---|---|
| | ($n$ = 29) | | | | |
| Mean MoCA–TS | 26.97 (2.01) | 26.45 (2.25) | 0.82 | 0.62–0.92 | < 0.001 |
| Mean MoCA–DS | | | | | |
| executive functioning | 1.79 (0.41) | 1.90 (0.31) | 0.53 | 0.03–0.78 | 0.022 |
| visuospatial abilities | 2.93 (1.00) | 2.83 (1.00) | 0.52 | −0.04–0.78 | 0.031 |
| attention | 5.86 (0.35) | 5.76 (0.44) | 0.38 | −0.30–0.71 | 0.104 |
| language | 4.59 (0.63) | 4.14 (0.58) | 0.44 | −0.09–0.73 | 0.026 |
| abstract reasoning | 1.76 (0.44) | 1.93 (0.26) | −0.29 | −1.56–0.38 | 0.761 |
| memory | 4.17 (0.85) | 4.00 (1.13) | 0.57 | 0.08–0.80 | 0.016 |
| orientation | 5.86 (0.35) | 5.90 (0.31) | −0.32 | −1.96–0.39 | 0.761 |
| Mean MoCA–MIS | 13.62 (1.50) | 13.72 (1.49) | 0.48 | −0.14–0.76 | 0.051 |
| Mean item scores[a] | | | | | |
| alternating trail making | 0.97 (0.19) | 0.97 (0.19) | 1.00 | – | – |
| copy figure | 0.38 (0.49) | 0.41 (0.50) | 0.13 | −0.93–0.60 | 0.367 |
| clock drawing | 2.55 (0.69) | 2.41 (0.73) | 0.62 | 0.20–0.82 | 0.006 |
| animal naming | 2.86 (0.35) | 2.97 (0.19) | −0.13 | −1.33–0.46 | 0.629 |
| digit span | 1.97 (0.19) | 1.86 (0.35) | 0.54 | 0.07–0.78 | 0.016 |
| sustained attention | 1.00 (0.00) | 0.97 (0.19) | 0.00 | −1.13–0.53 | 0.500 |
| serial subtraction | 2.90 (0.31) | 2.93 (0.26) | 0.52 | −0.03–0.78 | 0.030 |
| sentence repetition | 1.72 (0.46) | 1.17 (0.54) | 0.35 | −0.20–0.68 | 0.032 |
| verbal fluency | 0.83 (0.38) | 0.93 (0.26) | 0.35 | −0.34–0.69 | 0.123 |

Note: [a] = item scores for abstract reasoning, memory and orientation are not shown, as they are the same as the domain scores.

## Discussion

The current study assessed the psychometric properties of the original version and two alternate versions of the MoCA in a group of healthy participants with an age range of 18–70 years. We found that older participants performed worse on MoCA–TS and –MIS than younger participants, while participants with higher educational levels and a higher estimated premorbid intelligence also obtained higher MoCA scores. Significant but small sex differences were found for MoCA–MIS, with women outperforming men. Systematic differences between versions were identified for the items animal naming, sentence repetition and MoCA–DS language and abstract reasoning. The test–retest reliability for the MoCA–TS was good (7.1–7.2) to excellent (7.1–7.3). For the MoCA–MIS, the test–retest reliability was poor (7.1–7.2) to fair (7.1–7.3).

The current results show that performance on the MoCA is moderated by educational attainment, intelligence and age, and that these factors should be taken into account when interpreting results on this screener (Shulman, 2000). The effect of intelligence on MoCA performance was expected as it is known that intelligence typically correlates highly with level of education (Lezak et al., 2012), albeit that in older adults educational attainment and intelligence may not always correspond well because of limited access or possibilities to advanced schooling. Comparing our results of participants from a large age range with other studies shows they are in agreement with previous findings in adults aged 50 and older (Zheng et al., 2012; Sugarman et al., 2014; Malek–Ahmadi et al., 2015; Oren et al., 2015; Yancar Demir et al., 2015; Apolinario et al., 2018). Next, like several other studies, this study did not find an effect of sex on MoCA–TS (Zheng et al., 2012; Santangelo et al., 2015; Kopecek, Stepankova, et al., 2017; Apolinario et al., 2018). However, an effect of sex on the MoCA–MIS was found, in favour of women. Ojeda et al. (2016) also found an effect of sex on the delayed recall of the MoCA in Spanish participants aged ≥ 18. The difference between men and women in memory functioning has also been objectified in childhood ages (Gur et al., 2012) and in particular working memory tasks in adults (Saylik et al., 2018).

No systematic differences between MoCA–TS of the alternate versions compared to version 7.1 were found, indicating that all versions are essentially equivalent. This was also found for the recently developed MoCA–MIS, replicating the findings of Chertkow et al. (2011) and Nasreddine et al. (2016) in older individuals. Taking a closer look at the items, however, it was found that animal naming, sentence repetition and abstract reasoning did systematically differ between versions, with some items of the alternate versions being more difficult and others less compared to MoCA version 7.1. Lebedeva et al. (2016) reported similar findings for both animal naming and abstract reasoning. They also found a performance difference for the item figure copy across the different versions. The fact that we did not

identify any differences for the latter could be explained by the thorough checking of scores and the conservative scoring method that was used, eliminating ambiguities in scoring and possible inter–rater differences influencing results (Cumming et al., 2020). Similarly strict scoring criteria are embedded in the instructions of the recently published MoCA version 8 (i.e. 'all lines meet with little or no space' and 'the figure's orientation in space must be preserved'). The systematic differences found between the sentences may be the outcome of the adaptation and translation process into Dutch resulting in somewhat longer sentences for alternate versions 7.2 and 7.3 compared to the English–language alternate versions. Nasreddine et al. (2016) completely changed the sentences in the French versions instead of translating them from the original English–language versions. The systematic differences that were found on item level cancelled each other out when looking at the MoCA–TS, resulting in three equivalent versions. Focussing on the MoCA–DS, it should be taken into account that individuals may perform better on language (which includes the items animal naming and sentence repetition) and worse on abstract reasoning on version 7.1 compared to version 7.2 and/or 7.3 due to the abovementioned systematic differences, rather than actual changes in cognitive functioning over time.

A good to excellent test–retest reliability was found for MoCA–TS between versions 7.1–7.2 and 7.1–7.3, respectively, in line with findings of other studies (Costa et al., 2012; Feeney et al., 2016; Nasreddine et al., 2016; Kopecek, Bezdicek, et al., 2017; Wu et al., 2017). The test–retest reliabilities can be used to compute Reliable Change Indices (RCI; Chelune et al., 1993) making the MoCA scores useful for monitoring change over time. The MoCA–MIS had poor to fair test–retest reliability, possibly due to a strong negative skewness of scores with ceiling performances on both versions in 31 participants (as opposed to 0 ceiling performances for MoCA–TS on both versions). However, in memory impaired individuals, the MoCA–MIS has been found to be a useful index of monitoring change over time. For instance, Julayanont et al. (2014) showed that the MoCA–MIS was a good predictor for conversion from mild cognitive impairment to Alzheimer's disease. More research into the applicability of the MoCA–MIS in other clinical samples is needed, as compared to this sample of healthy individuals. For the other MoCA–DS and item scores, reliabilities ranged from poor to good, strengthening the fact that the MoCA is reliable and applicable as a global screen for cognitive functioning rather than as a tool to assess individual cognitive domains.

Some strengths of the study are firstly, that it is the first one to assess the psychometric properties of all three versions of the Dutch translations of the MoCA. Secondly, we included the MoCA–MIS for which not much is known yet about the applicability of this score in clinical practice. Next, it was possible to include a large sample of healthy participants with a wide age range (including adults aged 18–50), and educational background, being representative for the general population. And finally, although we used the Dutch version of the MoCA, our

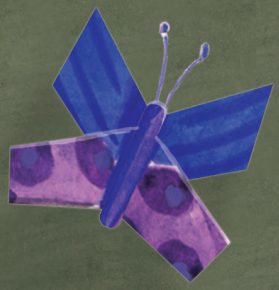
results are clearly also relevant for the use and interpretation of other–language versions of the MoCA. Limitations to the current study are, firstly, the non–orthogonal design, resulting in a relatively small group for comparing version 7.1 with version 7.3, and making it unable to compare version 7.2 with version 7.3, and secondly, that only self–reported exclusion criteria were used rather than an objective measure of cognitive impairment.

With respect to the clinical implications of our results, it is clear that an adjustment for education (either for level or years) is essential, as originally proposed by Nasreddine et al. (2005), and recently fine–grained by Bruijnen, Jansen, et al. (2019). However, further research is needed in order to examine if a better adjustment method can be generated. For instance, more elaborate stratified or regression–based normative data could be constructed, like those of Borland et al. (2017) who proposed normative Swedish data that adjust the total score for age, education and sex. Furthermore, it should be noted that a ceiling performance was found for a substantial number of healthy participants for the MoCA–MIS, indicating that this index may be insensitive to small cognitive decrements in some clinical populations.

Some of the shortcomings of MoCA version 7 might be overcome in the recently published version 8. When comparing the English–language versions 7 to versions 8, no changes were seen in version 1, while in versions 2 and 3 only about half of the items remained the same (i.e. the figures are all 'cube'–like, using only straight lines, and the digits are randomised rather than changed). For the Dutch translation, only version 8.1 has been made available yet, for which one word of the memory subtest was replaced. As for the scoring and administration instructions, changes have been made by clarifying some of the ambiguities in instructions that lead to personal interpretation in the scoring of version 7 (i.e. the possibility to repeat instructions, clarifications for scoring the executive/visuospatial items, simplified instructions for the verbal fluency, the adding of multiple–choice cues), but also the MoCA–MIS is included as a stand–alone score. If these changes/additions are, in fact, overcoming the shortcomings should be examined in more detail in future research, when MoCA version 8 becomes more widely available.

Based on both MoCA–TS and –MIS the Dutch translations of the MoCA are comparable to the English–language versions in their equivalence across versions and their test–retest reliability. Comparisons of the MoCA–DS should, however, be interpreted with caution. Although performance is affected by age, education and intelligence, adequate psychometric properties were found. The test–retest reliability can be used to determine change over time by calculating a reliable change index, adding to the clinical usability of the MoCA. After some training and following strict instructions the screener is easy to score, and was also reported as being acceptable in terms of clarity and difficulty for those undergoing it.

Een bijzonder dankjewel voor de ‘Korsakov Reünie’ meisjes, Jeanine, Josette, Laura, Iris, Moniek en Jolente, het wordt tijd dat we elkaar weer eens kunnen treffen voor een escape room of een lekkere high tea. Het is altijd gezellig met jullie en ik ben blij dat we contact zijn blijven houden door onze eigen drukke levens heen. Jullie zijn het bewijs dat je elkaar niet vaak hoeft te zien om het gezellig samen te hebben. De verbintenis die de Korsakov ons heeft gegeven, voelt elke keer een beetje als thuiskomen.



# Chapter 3

## The Montreal Cognitive Assessment (MoCA) as a cognitive screen in addiction health care: a validation study for clinical practice

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## Abstract

The current study assessed the criterion validity of the Montreal Cognitive Assessment (MoCA) as a short cognitive screen for use in addiction health care. Eighty–two patients were assessed with two parallel versions of the MoCA; at intake (baseline) and directly preceding an extensive neuropsychological assessment (NPA) approximately eight weeks later (follow–up). Of all included patients, 54.9% were classified as having substance–induced neurocognitive disorder. The most common primary substance of abuse was alcohol (70.7%). The criterion validity was determined predictively and concurrently, and sensitivities of 0.56 and 0.67 and specificities of 0.62 and 0.73 were found, respectively. While the MoCA is an adequate screen when administered at the same time as the NPA, the predictive validity of administering this cognitive screen at intake is limited. Furthermore, the relation between MoCA domain scores and the performance on their corresponding cognitive domain in the NPA is more reliable when the MoCA is administered at the same time as the NPA. While the MoCA can be used to screen for cognitive impairments in patients in addiction health care, the instrument's sensitivity is not optimal, which should be taken into account when interpreting results.

# Introduction

About 0.6% of the adult population worldwide (an estimated 29.5 million) suffer from substance use disorder (SUD; United Nations Office on Drugs and Crime, 2017). SUD affects the individual in social, physical and economical ways (Laudet et al., 2002) and may result in cognitive impairments interfering with treatment (Aharonovich et al., 2006; Bates et al., 2006; Copersino et al., 2012). The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM–5; APA, 2013) introduced the term 'neurocognitive disorder' (NCD) in which the subtype substance–induced NCD can be classified as either major or mild, based on severity and everyday limitations. Cognitive impairments in patients with SUD have an estimated prevalence of 30% – 80% (Copersino et al., 2009). The exact prevalence of substance–induced NCD is, however, difficult to establish based on the existing literature (Toledo–Fernández et al., 2018).

The effects of chronic substance use on cognitive functioning are both acute and chronic and vary across substances, resulting in decreased treatment adherence, lower self–efficacy and less treatment retention (Aharonovich et al., 2006; Bates et al., 2006; Copersino et al., 2012). Therefore, insight into an individual's cognitive functioning is crucial, as it enables to personalize and optimize treatment effectiveness (Allen et al., 1997; Sofuoglu et al., 2010; Bates et al., 2013). Often patients with SUD lack insight into their NCD, as indicated by a lack of correlation between objectively measured and subjectively experienced cognitive deficits (Horner et al., 1999; Walvoort et al., 2016). Although neurocognitive assessment can accurately detect the pattern and severity of cognitive impairment in patients with SUD, the administration of such an extensive neuropsychological assessment (NPA) is not always feasible. Therefore, this study investigated the validity of a short and easy–to–administer cognitive screen, the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), in patients with SUD.

Originally developed to detect mild cognitive impairment (MCI), the MoCA has also been found to be valid in SUD for detecting cognitive deficits (Copersino et al., 2009; Rojo–Mota et al., 2013; Ridley et al., 2018). However, only one study in patients with alcohol use disorders (AUD) has correlated the MoCA to the gold standard NPA performance (Ewert et al., 2018), with no studies in users of other substances.

The current prospective study assessed the criterion validity of the MoCA as a screen for cognitive impairment in a sample of patients with SUD. First, the optimal cut–off for use in addiction health care was established. Next, the criterion validity was assessed by comparing MoCA results with an extensive NPA. Additionally, the interaction of substance type, abstinence duration and MoCA performance has been examined. In order to maximize the external validity of the design, this study was designed to comply as much as possible with treatment as usual in all participating institutions.

# Methods

### Design

A prospective study was performed with two time points of assessment using two authorized and validated parallel versions of the MoCA (Costa et al., 2012). MoCA version 7.1 was administered at intake (baseline) and MoCA version 7.2 directly preceding the NPA at follow–up approximately eight weeks later. Data were collected between August 2012 and March 2015. The study was approved by the internal review boards of all participating health care centres and the research board of the Nijmegen Institute for Scientist–Practitioners in Addiction.

### Participants

The aim was to recruit a total of 100 outpatients seeking treatment for SUD from four participating addiction health care centres in the Netherlands (IrisZorg, Novadic–Kentron, Tactus and Vincent van Gogh Institute for Psychiatry). This study is part of a larger study ($N$ = 691), for which the inclusion criteria were 1) dependency or abuse of a substance (excluding nicotine) or behaviour; 2) age 18–75; and 3) signed informed consent for participation at baseline and/or follow–up. The exclusion criterion was an inability to administer the MoCA, due to for instance: a neurological (e.g. stroke, dementia, traumatic brain injury) or very unstable acute psychiatric disorder, severe lack of motivation, or insufficient Dutch language skills. Patients were included regardless of abstinence to increase the external validity of the design.

### Materials

*Montreal Cognitive Assessment*

The MoCA (Nasreddine et al., 2005) consists of 12 elements measuring seven cognitive domains. These domains include executive functioning; visuospatial abilities; attention, concentration and working memory (called 'attention' from now on); language; abstract reasoning; memory; and orientation. A total score is calculated, with a maximum of 30 points. Nasreddine et al. (2005) found a score of ≤ 25 to be indicative of MCI. However, several studies have identified different cut–off scores for different populations (Julayanont et al., 2013). The validity of the MoCA, including both alternate forms, has been established in detecting MCI, with sensitivities and specificities ranging from 0.90 to 1.00 and 0.57 to 0.62, respectively. Alternate–form reliability for healthy controls ranged from 0.52 to 0.69 and all versions were found to be equivalent in previous research (Costa et al., 2012; Nasreddine et al., 2016). The authorized Dutch translations of two parallel versions were used.

*Neuropsychological assessment*

The tests included in the NPA, that was administered at follow–up, were selected based on the cognitive domains targeted by the MoCA, thus assessing a broad range of cognitive functions. The allocation of the NPA (sub)tests and MoCA elements to each cognitive domain was based on DSM–5 criteria for NCD (APA, 2013, pp. 593–595) and is summarized in Table 3.1.

*Measurements in the addictions for triage and evaluation*

The Measurements in the Addictions for Triage and Evaluation (MATE 2.1; Schippers et al., 2011) is part of the intake procedure and consists of an interview and self–report questionnaires for collecting relevant patient characteristics. In this study, Section 1 'Substance use' and Section 3 'History of treatment for substance use disorders' were used.

### *Procedure*

At baseline, the MATE 2.1 was administered and written informed consent was obtained. MoCA version 7.1 was administered by trained professionals during intake procedure. For administration of the NPA (follow–up) an appointment approximately six to eight weeks later was made. The NPA procedure was fixed for all institutions and administration was done by trained psychologists. All professionals were trained in MoCA and/or NPA administration in accordance with the test manuals, by the coordinator of this study.

Recruitment for follow–up was based on random selection (i.e. one in eight patients of the large study were randomly selected for a follow–up), indication (i.e. based on care as usual), or both. Three patients with a behavioural disorder without substance use were excluded for this study. At follow–up, MoCA version 7.2 was administered preceding the NPA. Prior to both baseline and follow–up, a self–reported estimation of substance use in the week before administration, or abstinence duration (if > 7 days) was obtained.

### *Analyses*

*Patient characteristics*

For determining the presence of NCD, criteria for substance–induced NCD of the DSM–5 (APA, 2013) were combined with the 'cognitive impairment, no dementia' criteria as outlined in van den Berg et al. (2005). All raw scores of the NPA were transformed into standard *z*–scores, according to the normative data. These standard *z*–scores were classified as: 0 = average (≥ –1.00); –1 = below average (between –1.00 and –1.65); –2 = impaired (≤ –1.65). An average score for a domain of ≤ –1.00 was considered to be impaired. If at least two out of all seven NPA domains were impaired, the patient was classified as having substance–induced NCD. Nine patients had missing data in one or more NPA domain, but

the remaining results were sufficient to validly classify each patient. Mean NPA domain scores and patient characteristics were compared between patients with and without NCD by using independent *t*–tests, chi–square tests or Mann–Whitney *U*–tests (non–normal variables).

*Criterion validity*

Level of education was classified on a seven–point scale ranging from 1 = less than primary school to 7 = university degree or higher (Duits et al., 2014), a classification system comparable to the ISCED (UNESCO, 2012). As it was found that years of education affects performance on the MoCA (Nasreddine et al., 2005; Chertkow et al., 2011), Spearman's rho correlations were used to relate the unadjusted MoCA–TS at baseline and follow–up to this level of education. Based on the studies by Chertkow et al. (2011) and van der Elst et al. (2005), the MoCA–TS was then adjusted for education (low level of education, classifications 1, 2 and 3: two additional points; average level of education, classifications 4 and 5: one additional point; and highly educated patients, classifications 6 and 7: no additional points), with the maximum MoCA–TS remaining 30 in all cases. MoCA results were then explored and differences between patients with and without NCD were computed using independent *t*–tests. Furthermore, MoCA–DS were correlated with mean *z*–scores on the corresponding NPA domain, and systematic differences between MoCA–DS and –TS at baseline and at follow–up were assessed with paired *t*–tests.

The predictive validity was assessed by computing a receiver operating characteristic (ROC) curve with the corresponding area under the curve (AUC) for the MoCA–TS at baseline, with NPA classification (NCD or no–NCD) at follow–up as a criterion. The cut–off point was determined by the optimal sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). After applying the cut–off to the data, overall agreement and chance–adjusted agreement (Cohen's kappa) were determined. The concurrent validity was assessed in the same way as the predictive validity by using MoCA and NPA results at follow–up.

*Substance type and abstinence duration*

The influence of substance type and abstinence duration on MoCA performance at follow–up was estimated using logistic regression with abstinence duration, substance type (alcohol versus other drugs), MoCA–TS, and interactions between each as predictors, with NCD classification (NCD versus no–NCD) as the dependent variable. The Outlier Labelling Rule (Hoaglin & Iglewicz, 1987) was used to exclude outliers, leading to the exclusion of one outlier for abstinence duration. All data were computed and analysed with IBM SPSS version 24.0.

***Table 3.1.*** Cognitive domains with the corresponding elements of the Montreal Cognitive Assessment (MoCA) and (sub)tests of the neuropsychological assessment (NPA).

| Cognitive domain | MoCA item (score range) | NPA element (used score) |
|---|---|---|
| Executive functioning | Alternating Trail Making (0–1) | D–KEFS TMT |
| | Verbal Fluency (0–1) | Letter–number switching (scaled score) |
| | | Number sequencing (scaled contrast score*) |
| | | Letter sequencing (scaled contrast score*) |
| | | Stroop CWT |
| | | Interference score (*t*–score) |
| Visuospatial abilities | Figure Copy (0–1) | WAIS–IV–NL |
| | Clock Drawing (0–3) | Block design (scaled score) |
| | | RCFT |
| | | Copy (*t*–score) |
| Attention | Digit Span (0–2) | WAIS–IV–NL |
| | Sustained Attention (0–1) | Digit span forward (scaled score) |
| | Serial Subtraction (0–3) | Digit span backward (scaled score) |
| Language | Naming (0–3) | – |
| | Sentence Repetition (0–2) | |
| Abstract reasoning | Abstraction (0–2) | WAIS–IV–NL |
| | | Similarities (scaled score) |
| | | NART (deviation IQ) |
| Memory | Delayed Recall (0–5) | RAVLT |
| | | Total correct (*t*–score) |
| | | Delayed recall (*t*–score) |
| | | RCFT |
| | | Immediate reproduction (*t*–score) |
| Orientation | Orientation (0–6) | CST–14 (raw score) |
| Processing speed | – | Stroop CWT |
| | | Word reading (*t*–score) |
| | | Colour naming (*t*–score) |
| | | D–KEFS TMT |
| | | Motor speed (scaled score) |

Note: D–KEFS TMT = Delis–Kaplan Executive Function System – Trail Making Test (Delis et al., 2007); Stroop CWT = Stroop Colour Word Test (Hammes, 1971); WAIS–IV–NL = Wechsler Adult Intelligence Scale IV – Dutch (Wechsler, 2012); RCFT = Rey–Osterrieth Complex Figure Test (Meyers & Meyers, 1995); NART = National Adult Reading Test (Schmand et al., 1992); RAVLT = Rey Auditory Verbal Learning Test (Saan & Deelman, 1986); CST–14 = Cognitive Screening Test – 14 (de Graaf & Deelman, 1991); * = Scaled score obtained by contrasting performance on the number sequencing and letter sequencing conditions against performance on the number–letter switching condition.

# Results

### *Patient characteristics*

A total of 82 patients were included in this study, 54.9% of whom were classified as having NCD based on the NPA results. Mean NPA domain scores differed significantly between patients with and without NCD for all cognitive domains except orientation (Table 3.2).

***Table 3.2.*** Mean (*SD*) performance in *z*–scores for each domain of the neuropsychological assessment (NPA) for patients with and without neurocognitive disorders (NCD) and in the total sample.

| NPA domain | Total (*n* = 82) | NCD (*n* = 45) | no–NCD (*n* = 37) | *p*–value |
|---|---|---|---|---|
| Executive functioning | –0.10 (0.89) | –0.32 (1.02) | 0.16 (0.62) | .011* |
| Visuospatial abilities | –0.83 (0.99) | –1.21 (0.88) | –0.37 (0.92) | < .001*** |
| Attention | –0.78 (0.90) | –1.16 (0.71) | –0.32 (0.89) | < .001*** |
| Abstract reasoning | –0.71 (0.83) | –1.00 (0.85) | –0.35 (0.64) | < .001*** |
| Memory | –0.67 (1.01) | –1.00 (1.02) | –0.27 (0.86) | .001** |
| Orientation | 4.20 (1.11) | 4.05 (1.32) | 4.36 (0.80) | .211 |
| Processing speed | –0.61 (0.89) | –1.03 (0.80) | –0.10 (0.71) | < .001*** |

Note: * = $p < .05$; ** = $p < .01$; *** = $p < .001$.

The overall mean age was 44.1 (*SD* = 13.77) and 68.3% were men. The most prevalent primary problem substance of abuse was alcohol (70.7%). More patients were abstinent at follow–up than at baseline (an increase of 28.0%). The majority (42.7%) was not abstinent at either time point. Except for age and marital status, both patient groups were comparable (Table 3.3).

***Table 3.3.*** Patient characteristics for patients with and without neurocognitive disorders (NCD) and in the total sample.

| | Total (*n* = 82) | NCD (*n* = 45) | no–NCD (*n* = 37) | *p*–value |
|---|---|---|---|---|
| Mean age in years (*SD*) | 44.1 (13.8) | 46.9 (13.9) | 40.8 (13.0) | .045* |
| Sex, men (%) | 56 (68.3) | 30 (66.7) | 26 (70.3) | .814# |
| Level of Education (%) | | | | .251 |
| low educated | 14 (17.1) | 5 (11.1) | 9 (24.3) | |
| average educated | 59 (72.0) | 34 (75.6) | 25 (67.6) | |
| high educated | 9 (11.0) | 6 (13.3) | 3 (8.1) | |

***Table 3.3.*** Continued.

| | Total ($n$ = 82) | NCD ($n$ = 45) | no–NCD ($n$ = 37) | $p$–value |
|---|---|---|---|---|
| Marital Status (%) | | | | .028* |
| single | 26 (31.7) | 12 (26.7) | 14 (37.8) | |
| with partner/married | 34 (41.5) | 15 (33.3) | 19 (51.4) | |
| separated/divorced | 20 (24.4) | 16 (35.6) | 4 (10.8) | |
| widowed | 2 (2.4) | 2 (4.4) | 0 (0.0) | |
| Inclusion based on (%) | | | | .179 |
| indication | 59 (72.0) | 35 (77.8) | 24 (64.9) | |
| selection | 17 (20.7) | 6 (13.3) | 11 (29.7) | |
| both | 6 (7.3) | 4 (8.9) | 2 (5.4) | |
| Primary problem substance (%) | | | | .864 |
| alcohol | 58 (70.7) | 33 (73.3) | 25 (67.6) | |
| cannabis | 13 (15.9) | 6 (13.3) | 7 (18.9) | |
| stimulants | 8 (9.8) | 4 (8.9) | 4 (10.8) | |
| opiates | 3 (3.7) | 2 (4.4) | 1 (2.7) | |
| Abstinent, yes (%) | | | | |
| at baseline | 20 (75.6) | 13 (28.9) | 7 (18.9) | .317# |
| mean duration in days ($SD$) | 44.9 (77.8) | 23.5 (12.6) | 84.4 (126.5) | .141‡ |
| at follow–up | 43 (52.4) | 26 (57.8) | 17 (45.9) | .375# |
| mean duration in days ($SD$) | 62.7 (45.4) | 62.6 (45.4) | 62.9 (46.8) | .950‡ |
| Abstinent at (%) | | | | .604 |
| baseline, not follow–up | 4 (4.9) | 2 (4.4) | 2 (5.4) | |
| follow–up, not baseline | 27 (32.9) | 15 (33.3) | 12 (32.4) | |
| both baseline and follow–up | 16 (19.5) | 11 (24.4) | 5 (13.5) | |
| neither baseline nor follow–up | 35 (42.7) | 17 (37.8) | 18 (48.6) | |
| Mean interval between baseline and follow–up in days ($SD$) | 92.9 (83.6) | 104.0 (101.0) | 79.5 (54.04) | .394‡ |
| History of treatment, yes (%) | 41 (50.0) | 24 (53.3) | 17 (45.9) | .657# |

Note: # = Fisher's Exact Test; ‡ = Mann–Whitney $U$–test; * = $p < .05$.

### *Criterion validity*

*Montreal Cognitive Assessment*

Level of education correlated with the unadjusted MoCA–TS both at baseline ($\rho$ = 0.421, $p < .001$) and at follow–up ($\rho$ = 0.550, $p < .001$).

Patients with NCD performed significantly worse on the MoCA than patients without NCD, both at baseline and at follow–up. The same was true for the MoCA–DS executive functioning. At baseline, the difference in performance on the MoCA–DS memory was also significant, while performance on the MoCA–DS language and abstract reasoning differed significantly between both patient groups at follow–up. Performance on the other MoCA–DS did not differ significantly between both patient groups (Table 3.4).

***Table 3.4.*** Mean (*SD*) and *t*–test results for Montreal Cognitive Assessment (MoCA) domain (MoCA–DS) and total scores (MoCA–TS) at baseline and follow–up, for patients with and without neurocognitive disorders (NCD) and for the total sample.

| MoCA–DS | | Total | NCD | no–NCD | *t*(80) |
|---|---|---|---|---|---|
| | | (*n* = 82) | (*n* = 45) | (*n* = 37) | (*p*–value) |
| Executive functioning | B | 1.02 (0.70) | 0.82 (0.65) | 1.27 (0.69) | 3.02 (.003*) |
| | F | 1.38 (0.60) | 1.22 (0.60) | 1.57 (0.56) | 2.69 (.009*) |
| | *t*(81) | –4.89 (< .001***) | | | |
| Visuospatial abilities | B | 2.49 (0.93) | 2.40 (0.96) | 2.59 (0.90) | 0.94 (.350) |
| | F | 2.99 (0.91) | 2.82 (0.96) | 3.19 (0.81) | 1.85 (.069) |
| | *t*(81) | –4.33 (< .001***) | | | |
| Attention | B | 5.09 (1.15) | 4.89 (1.25) | 5.32 (0.97) | 1.73 (.087) |
| | F | 5.49 (0.79) | 5.36 (0.91) | 5.65 (0.59) | 1.76 (.082) |
| | *t*(81) | –3.22 (.002**) | | | |
| Language | B | 4.27 (0.79) | 4.27 (0.78) | 4.27 (0.80) | 0.02 (.984) |
| | F | 3.61 (1.04) | 3.40 (1.03) | 3.86 (1.00) | 2.06 (.043*) |
| | *t*(81) | 5.36 (< .001***) | | | |
| Abstract reasoning | B | 1.30 (0.75) | 1.24 (0.74) | 1.38 (0.76) | 0.81 (.423) |
| | F | 1.41 (0.68) | 1.24 (0.74) | 1.62 (0.55) | 2.65 (.010*) |
| | *t*(81) | –1.10 (.274) | | | |
| Memory | B | 2.93 (1.62) | 2.53 (1.65) | 3.41 (1.46) | 2.51 (.014*) |
| | F | 3.11 (1.60) | 2.82 (1.68) | 3.46 (1.45) | 1.82 (.073) |
| | *t*(81) | –1.06 (.293) | | | |
| Orientation | B | 5.62 (0.68) | 5.64 (0.68) | 5.59 (0.69) | –0.33 (.743) |
| | F | 5.78 (0.47) | 5.76 (0.53) | 5.81 (0.40) | 0.53 (.601) |
| | *t*(81) | –1.89 (.063) | | | |
| MoCA–TS | B | 23.78 (3.37) | 22.78 (3.64) | 25.00 (2.57) | 3.23 (.002*) |
| | F | 24.83 (3.31) | 23.60 (3.45) | 26.32 (2.43) | 4.19 (< .001***) |
| | *t*(81) | –3.33 (.001**) | | | |

Note: B = baseline; F = follow–up; * = $p < .05$; ** = $p < .01$; *** = $p < .001$.

At baseline, correlations between performance on the MoCA and NPA were significant for the MoCA–DS executive functioning ($r$ = 0.238, $p$ = .032), abstract reasoning ($r$ = 0.300, $p$ = .006), and memory ($r$ = 0.423, $p$ < .001). At follow–up, there was an almost perfect correspondence between MoCA and NPA performance: all MoCA–DS were significantly correlated to the corresponding NPA domain (executive functioning: $r$ = 0.328, $p$ = .003; visuospatial abilities: $r$ = 0.241, $p$ = .029; attention: $r$ = 0.396, $p$ < .001; abstract reasoning: $r$ = 0.542, $p$ < .001; memory: $r$ = 0.455, $p$ < .001; orientation: $r$ = 0.229, $p$ = .043).

*Predictive validity at baseline*

An AUC value of 0.676 was found ($p$ = .006; Figure 3.1) and a cut–off score of 24 yielded the most optimal sensitivity (0.56), specificity (0.62), PPV (64.1%), and NPV (53.5%), using the NPA as gold standard. Applying this cut–off score, 39 out of 82 patients were classified as having NCD, while 45 out of 82 patients were classified as having NCD based on the NPA. The overall agreement with the NPA was 58.5% and the chance–adjusted agreement was 17.5% (Table 3.5).

*Concurrent validity at follow–up*

An AUC of 0.745 was found ($p$ < .001; Figure 3.1) and a cut–off score of 25 yielded the most optimal sensitivity (0.67), specificity (0.73), PPV (75.0%), and NPV (64.3%), using the NPA as gold standard. Applying this cut–off score, 40 out of 82 patients were classified as having NCD. The overall agreement with the NPA was 69.5% and the chance–adjusted agreement was 39.2% (Table 3.5).

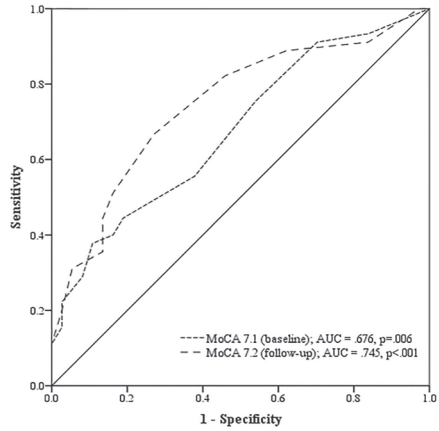



***Figure 3.1.*** Receiver Operator Characteristic (ROC) curve for the Montreal Cognitive Assessment (MoCA) total score at baseline and follow–up, using several cut–off points in comparison with neurocognitive disorders (NCD versus no–NCD); AUC = Area Under the Curve.

***Table 3.5.*** Relation between Montreal Cognitive Assessment total score (MoCA–TS) and neurocognitive disorders (NCD or no–NCD), at baseline and follow–up. Statistical significance of the Area Under the Curve (AUC) is reported.

| | MoCA at baseline | | MoCA at follow–up | |
|---|---|---|---|---|
| AUC (SE) | .676 (.059) | | .745 (.055) | |
| *p*–value | .006** | | < .001*** | |
| Cut–off (≤) | Sensitivity | Specificity | Sensitivity | Specificity |
| 20 | .289 | .919 | .200 | .973 |
| 21 | .378 | .892 | .311 | .946 |
| 22 | .400 | .838 | .356 | .865 |
| 23 | .444 | .811 | .444 | .865 |
| 24 | .556# | .622# | .511 | .838 |
| 25 | .756 | .459 | .667# | .730# |
| 26 | .911 | .297 | .822 | .541 |
| 27 | .933 | .162 | .889 | .378 |
| PPV (%) at # | 64.1 | | 75.0 | |
| NPV (%) at # | 53.5 | | 64.3 | |
| Accuracy (%) at # | 58.5 | | 69.5 | |
| Cohen's Kappa (%) at # | 17.5 | | 39.2 | |
| ≤ optimal cut–off (*n*, %) | 39 (47.6) | | 40 (48.8) | |

Note: # = MoCA cut–off with most optimal sensitivity and specificity; PPV = positive predictive value; NPV = negative predictive value; * = $p < .05$; ** = $p < .01$; *** = $p < .001$.

*Systematic differences between MoCA versions 7.1 and 7.2*

Paired *t*–tests between MoCA results for version 7.1 (baseline) and 7.2 (follow–up) showed that only the MoCA–DS abstract reasoning, memory, and orientation did not differ significantly. Scores on all other MoCA–DS and the MoCA–TS differed significantly between both versions. For all MoCA–DS except language, mean scores on MoCA version 7.2 were higher (Table 3.4).

*Substance type and abstinence duration*

The logistic regression model was statistically significant ($\chi^2(7) = 16.58$, $p = .020$), correctly classifying 69.0% of cases. However, neither the predictors nor any interaction between the predictors in the model were statistically significant.

## Discussion

This study is the first to examine the MoCA as a short cognitive screen in a sample of patients with SUD, using an extensive NPA as benchmark. The results show that administration of the MoCA at baseline resulted in a worse validity than the MoCA administered at follow–up. Also, while at follow–up all MoCA–DS correlated with the corresponding domain of the NPA, at baseline only the MoCA–DS executive functioning, abstract reasoning, and memory significantly predicted NPA performance eight weeks later.

These findings are partly in line with other MoCA studies (Wester et al., 2013; Oudman et al., 2014; Alarcon et al., 2015) where only Alarcon et al. (2015) reported a higher predictive validity. There are, however, important differences between these studies and the current. First, only homogeneous groups of patients with AUD were included in previous studies, limiting their external validity. Second, patients in those studies were abstinent for at least one week (Alarcon et al., 2015) to a minimum of six months (Oudman et al., 2014), while in clinical practice patients are often not abstinent at intake. To date, only one study in AUD related MoCA performance directly to an NPA (Ewert et al., 2018), which is considered to be the gold standard for the assessment of cognitive impairments (Lezak et al., 2012). Ewert et al. (2018) found a higher education–adjusted cut–off score than was currently found to be indicative of cognitive impairment, using a homogeneous group of hospitalized patients with AUD. The only study in a heterogeneous group of patients with SUD (Copersino et al., 2009) was more in line with the present findings – albeit that slightly better psychometric properties were found.

Regarding the relation between MoCA–DS at baseline and NPA domain performance at follow–up, caution should be taken when interpreting the MoCA–DS. This is in line with a previous study also showing MoCA–DS to be poor predictors of impairment on neuropsychological tests (Moafmashhadi & Koski, 2013). The difference in findings between the predictive and concurrent validity can be explained by the interval between baseline and follow–up. Abstinence could also be an explanation as cognitive recovery is likely to occur with sustained abstinence in AUD (van Holst et al., 2011; Stavro et al., 2013), cannabis (Lyons et al., 2004), and stimulants (Iudicello et al., 2010; Vonmoos et al., 2014; Wood et al., 2014; Zhong et al., 2016). Although more patients were abstinent at follow–up, we did not find a significant effect of abstinence on MoCA performance in our statistical model.

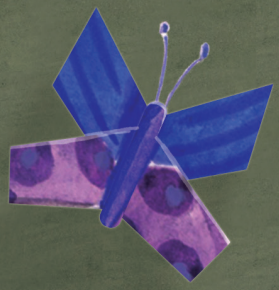
There are several strengths to the current study. First, the heterogeneity of the sample largely represents clinical practice, which makes the results generalizable to addiction health care. Second, the used adjustment method for level of education (based on Chertkow et al., 2011) is more fine–grained than the original adjustment method by Nasreddine et al.

(2005). Third, the extensive gold standard NPA, using widely used, valid and reliable tests, made analysis of specific domains and comparisons between patients with or without NCD possible, which has not been done before in a heterogeneous group of patients with SUD. Fourth, parallel MoCA versions were administered at two time points, which made it possible to assess validity predictively and concurrently. Finally, the effects of substance type and abstinence duration on MoCA performance were taken into account.

Although a moderate concurrent validity of the MoCA as compared to the NPA was found, it should be stressed that using a MoCA cut–off score of 25 results in only 66.7% of patients with NCD being classified correctly. Therefore, we underscore the fact that the MoCA as a screen can never substitute an extensive NPA. Therefore, a subsequent extensive NPA is recommended, especially in patients who perform above or at the cut–off point, given the low sensitivity.

Dan komen we bij de (oud–)leden van het NISPA, ook hier ga ik zeker namen vergeten, maar wil ik toch een poging doen: allereerst natuurlijk Cor, Boukje, Arnt, Dory en Sanne, bedankt voor alle mogelijkheden en ondersteuning, ook tijdens de NISPA–dagen.

Dan de collega onderzoekers, sommigen (inmiddels) zelf gepromoveerd, anderen bijna zover: Marike, Marion, Elke, Joanneke, Harmen, Rachel, Wiebren, Evelien, Hein, Peter, Maarten, Rouhollah en iedereen die ik bij naam vergeten mocht zijn. Het is mooi hoe NISPA zoveel onderzoekers uit verschillende regionen bij elkaar en tot elkaar weet te brengen. Vooral de schrijfdagen in het prachtige Huisen en de schrijfmiddagen gevolgd met pizza en een film waren altijd een inspiratie. Ik heb veel verhalen met jullie gedeeld en het was elke keer opnieuw op en top gezellig. Ik ben benieuwd of de film de volgende keer wel direct werkt zoals het hoort.



# Chapter 4

## Prevalence of cognitive impairment in patients with substance use disorder

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## Abstract

Cognitive impairments in substance use disorder predict treatment outcome and are assumed to differ between substances. They often go undetected, thus the current study focuses on the prevalence of and differences in cognitive functioning across substances by means of a cognitive screen at the early stage of addiction treatment. The Montreal Cognitive Assessment (MoCA) was administered to outpatients seeking treatment for substance use disorder. Patient characteristics (age, years of regular use, polysubstance use, severity of dependence/abuse, depression, anxiety and stress) were also taken into account. A total of 656 patients were included ($n$ = 391 used alcohol, $n$ = 123 used cannabis, $n$ = 100 used stimulants and $n$ = 26 used opioids). The prevalence of cognitive impairments was 31%. Patients using alcohol had a lower total– and memory domain score than those using cannabis. Patients using opioids scored lower on visuospatial abilities than those using cannabis or stimulants. Younger patients scored higher than older patients. No effect was found for the other investigated characteristics. Given the high prevalence of cognitive impairments, standard screening at an early stage of treatment is important to determine the course of treatment and maximise treatment outcome. Caution is needed in interpreting results about opioids due to an underrepresentation of this patient group, and more research is needed on the effect of age on MoCA performance.

# Introduction

Substance use disorder (SUD) refers to 'a cluster of cognitive, behavioural and physiological symptoms indicating that the individual continues using the substance despite significant substance–related problems' (APA, 2013, p. 483). Substances like alcohol, cannabis, stimulants and opioids are psychoactive drugs that may change brain function and structure after chronic use, and result in cognitive and behavioural deficits that remain even after detoxification. The prevalence of cognitive impairments in patients with SUD is still unclear (Toledo–Fernández et al., 2018) and is estimated between 30% and 80% (Copersino et al., 2009). This wide range includes, for instance, differences in the mode of action between substances, years and amount of regular use, and effects of sex. As each substance has different effects on brain functioning the consequences of prolonged substance use, such as cognitive impairments, will also differ between substances.

Acute alcohol intoxication primarily acts upon cognitive functions associated with the prefrontal cortex, such as planning, verbal fluency, memory and complex motor control (Peterson et al., 1990; Lyvers et al., 2010). The effects of alcohol on cognitive functioning post–detoxification are found to affect all cognitive domains (Stavro et al., 2013). After one to three weeks of abstinence, chronic alcohol use is still associated with decrements in memory, visuospatial abilities and inhibition (van Holst et al., 2011). After six months of abstinence, cognitive recovery generally has occurred (Pitel et al., 2009) but impairments have still been demonstrated in the domains of visuospatial abilities and decision making (Fernández–Serrano et al., 2011) which may last at least up to one year after abstinence (van Holst et al., 2011; Stavro et al., 2013). There is some evidence that in the long term, the cognitive consequences of alcohol use disorder (AUD) may be fully reversible (Arts et al., 2017), but cases of persistent cognitive impairments like Korsakoff's syndrome are not uncommon (Bowden, 1992).

The acute consequences of cannabis intoxication primarily involve working memory, executive functioning and attention (Lundqvist, 2005). Post–detoxification effects have been found to impact executive functioning after 17 hours until up to 21 days of abstinence (Pope Jr et al., 2001; Solowij et al., 2002; Crean et al., 2011). In the long term (i.e. after more than one month of abstinence), full cognitive recovery can occur (Pope Jr et al., 2001; van Holst et al., 2011; Gonzalez et al., 2017).

Concerning stimulant abuse, including cocaine, amphetamine and ecstasy, cognitive impairments are considered relatively mild (Goldstein et al., 2004) and seem to follow an inverted U–shape (Wood et al., 2014). Acute intoxication with low doses has mostly enhancing effects on response inhibition, attentiveness, speed and psychomotor

performance (Scott et al., 2007; Spronk et al., 2013). Cognitive impairments that occur after short–term abstinence in executive functioning, inhibition, (verbal) memory, psychomotor functions and attention disappear again after long–term remission (Jovanovski et al., 2005; Scott et al., 2007; Woicik et al., 2009; van Holst et al., 2011; Spronk et al., 2013; Schulte et al., 2014; Zhong et al., 2016). After one year of complete abstinence cognitive function has been found to be at the level of healthy controls (Iudicello et al., 2010; Vonmoos et al., 2014). There are case studies, however, that report major cognitive impairments in patients with a history of chronic stimulant use, with dosage being the critical determinant (Spronk et al., 2013; Wood et al., 2014; Jacobs et al., 2016).

Regarding opioid abuse, relatively few studies have assessed the acute cognitive sequelae. There is, however, ample evidence of impairments in the memory domain (Gruber et al., 2007), and impairments are also found after short–term abstinence in executive functioning, such as verbal fluency, inhibition and decision–making. These impairments have been demonstrated after up to one year of abstinence (van Holst et al., 2011). Whether full recovery occurs is largely unknown, although it has been found that at least some recovery is possible after long term abstinence of opioid abuse (Davis et al., 2002).

Cognitive deficits in chronic substance abuse are clinically relevant, as they affect treatment outcome and predict dropout rates as compared to cognitively intact users (Teichner et al., 2002). In AUD, cognitive impairments are associated with worse treatment compliance and lower self–efficacy, which in turn result in a drinking outcome with fewer abstinent days and more drinks per drinking day (Bates et al., 2006; Walvoort et al., 2016). Poorer treatment outcomes, lower treatment retention and less abstinence are also found in cocaine users with mild cognitive impairments (Aharonovich et al., 2003; Aharonovich et al., 2006). Poor executive function performance is associated with worse recognition of problem use and hampers the intention to stop using in both opioid and cocaine users (Yücel & Lubman, 2007; Severtson et al., 2010). Interventions targeting cognitive functioning, or taking cognitive impairments into account, may lead to a better treatment outcome both regarding the addiction and in everyday functioning (Forsberg et al., 1987; Roehrich et al., 1993).

Although the literature carefully suggests that full recovery of cognitive impairments may be possible for all substances, the influence of cognitive impairments on treatment outcome shows the importance of detecting these impairments for each individual at an early stage, so that personalised treatment can be implemented. The current study focuses on the prevalence of cognitive impairments and differences in cognitive functioning across substances by means of a cognitive screen, the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) at the early stage of addiction treatment right before interventions

are being initiated. The first aim is to determine, at intake, the prevalence of cognitive impairments in patients using different substances. Differences in cognitive performance across substances will be studied per cognitive domain. The second aim is to investigate the effects of age, abstinence (i.e. not having used prior to MoCA assessment classified as < 7 days, 7–41 days or ≥ 42 days), abstinence duration (i.e. number of days abstinent prior to MoCA assessment, with a minimum of seven days), polysubstance use, duration of regular use, severity of dependence/abuse, depression, anxiety and stress on cognitive functioning.

# Methods

### *Design*

A cross–sectional study was performed in which a validated cognitive screening instrument was administered as part of the intake procedure that contains items covering all cognitive domains, the MoCA (Nasreddine et al., 2005). Data were collected between April 2012 and December 2014 in four addiction health care centres. The study was approved by the internal review boards of all participating health care centres and the research board of the Nijmegen Institute for Scientist–Practitioners in Addiction.

### *Participants*

The aim was to include a total of 800 participants seeking treatment for SUD in one of four addiction health care centres in the Netherlands (IrisZorg, Novadic–Kentron, Tactus and Vincent van Gogh Institute for Psychiatry). The inclusion criteria were 1) dependency or abuse of a substance (excluding nicotine) or behaviour; 2) age 18–75; and 3) signed informed consent for participation. The only exclusion criterion was an inability to administer the MoCA, due to for instance a neurological (e.g. stroke, dementia, traumatic brain injury) or very instable acute psychiatric disorder, severe lack of motivation or insufficient Dutch language skills. Patients were included regardless of substance use status to comply as much as possible with treatment as usual in all participating institutions and to maximize the generalisability of the sample in relation to the population that is referred to addiction clinics in general.

### *Materials*

*Measurements in the Addictions for Triage and Evaluation*

The Measurements in the Addictions for Triage and Evaluation (MATE 2.1; Schippers et al., 2011) consists of an interview and self–report questionnaires for collecting information relevant for treatment purposes. In this study four sections were used. Section 1 'Substance use', is an interview that assesses the use of nine psychoactive substances and behavioural addictions in the past 30 days as well as lifetime. The primary–problem substance is determined by both the patient and the assessor as the substance that causes the most problems. For the current study, a participant was considered a polysubstance user if any substance other than the primary–problem substance, had a lifetime use of one year or longer, excluding nicotine and behavioural addictions. Section 3 'History of treatment for substance use disorders', assesses if a patient has ever been in treatment for addiction. Section 4 'Substance dependence and abuse', Section Alcohol & Drugs of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1997), is an interview questionnaire that helps to diagnose substance abuse or dependence by answering 11 yes or no questions about the primary–problem substance. Nine out of 11 questions are

used to determine severity of the addiction, with a maximum score of 9. Finally, section Q2 the Depression, Anxiety and Stress Scale (DASS–21; Lovibond & Lovibond, 1995; de Beurs, 2010), is a self–report questionnaire that measures symptoms of depression, anxiety and stress by answering 21 questions on a four–point scale (anchored with 0 = 'Did not apply to me at all' and 3 = 'Applied to me very much, or most of the time'), and is used to identify psychiatric comorbidity. The sum of all 21 questions multiplied by two, gives the DASS–21 total score, with a maximum of 126.

*Montreal Cognitive Assessment*

The MoCA (Nasreddine et al., 2005) consists of 12 items measuring seven cognitive domains: executive functioning; visuospatial abilities; attention, concentration and working memory (referred to as 'attention' from now on); language; abstract reasoning; memory; and orientation. The authorised Dutch translation of MoCA version 7.1 was used in this study. Administration of the MoCA takes approximately 15 minutes and scoring can mostly be done during administration. A total score is calculated by summing scores on all items, with a maximum of 30 points, where higher scores represent better cognitive performance. An adjustment for level of education is applied in which participants with a low level of education are awarded two extra points and participants with an average level of education are awarded one extra point, maintaining the maximum score of 30 (Chertkow et al., 2011). In addiction care, an optimal cut–off score of 24 was found to be predictive of substance–induced cognitive impairments, with a sensitivity of 0.56 and a specificity of 0.62, using an extensive neuropsychological assessment as gold standard (Bruijnen, Jansen, et al., 2019).

***Procedure***

As part of the intake procedure, the MATE 2.1 was administered to each participant seeking treatment. After the intake, participants were informed about the study. Written informed consent was required for participation and for using information of the administered MATE 2.1. MoCA version 7.1 was administered by professionals (e.g. psychologists, social psychiatric nurses, social workers) immediately or in the following appointment. All professionals were trained in MoCA administration and scoring by the psychologist coordinating this study in accordance with the formal instructions and based on experience of the psychologist for ambiguities that are not clarified in these instructions. Patients provided demographic information, such as sex, age, level of education, marital status and employment. Also, self–reported use of the primary–problem substance in the week before MoCA administration, or abstinence duration (if > 7 days) was recorded.

***Analyses***

For descriptive purposes, differences in patient characteristics between subgroups and between the four addiction health care centres were explored using chi–square tests and univariate analyses of variance (ANOVA). Second, the prevalence of cognitive impairments was calculated for the total sample and per primary–problem substance. Third, MoCA total and domain scores (MoCA–TS and –DS) for the total sample and differences between primary–problem substances were analysed using univariate and multivariate ANOVAs, respectively. Finally, the effects of age, years of regular use, abstinence duration in days, severity of dependence and/or abuse (Section Alcohol & Drugs of the Composite International Diagnostic Interview), and depression, anxiety and stress (DASS–21) on MoCA total score were examined by Pearson correlations; abstinence (< 7 days/7–41 days/≥ 42 days, Walvoort et al., 2013) with a univariate ANOVA; and the effect of polysubstance use (yes/no) on the MoCA–TS was examined with an independent *t*–test. Hochberg's GT2 (unequal sample sizes) or Games–Howell post–hoc tests (nonhomogeneous population variances) were used as post–hoc analyses in all ANOVAs. Alpha was set at 0.05 for all analyses and all data were computed and analysed using IBM SPSS version 25.0.

# Results

### *Patient characteristics*

A total of 656 patients was included (77% male). The mean age was 40 years (*SD* = 13.9). The most prevalent primary–problem substance was alcohol (60%), followed by cannabis (19%), stimulants (15%) and opioids (4%). Only six patients primarily used sedatives and another ten used GHB as the primary–problem substance (2%). Due to these small numbers, these patients were only included in analyses regarding the total sample. Patient characteristics differed significantly between patients with different primary–problem substances, except for the MATE 2.1 subscales depression and anxiety (Table 4.1). Between patients from all four health care centres, there were significant differences for primary–problem substance, marital status, abstinence, depression, stress and DASS–21 total score.

### *Cognitive impairments*

In the current sample, 206 patients (31%) performed below the MoCA cut–off score of 24. Per primary–problem substance, the prevalence was 34% for alcohol, 21% for cannabis, 27% for stimulants and 38% for opioids. Post–hoc tests revealed that only patients using alcohol performed significantly worse on the MoCA–TS than those using cannabis (Table 4.2). However, taking into consideration the sensitivity and specificity of the MoCA in addiction care (Bruijnen, Jansen, et al., 2019), a rather high proportion of patients with actual cognitive impairments may remain undetected, while at the same time cognitively intact patients are classified as being cognitively impaired by the MoCA.

### *Differences between primary–problem substances for cognitive domains*

Of all the possible differences that could be found between the primary–problem substances in performance on the MoCA–DS, only three were significant. Patients using alcohol performed significantly worse on memory than those using cannabis (*M*diff = 0.44, *SD* = 0.14, $p$ = 0.008). Patients using opioids performed significantly worse on visuospatial abilities than those using cannabis (*M*diff = 0.64, *SD* = 0.20, $p$ = 0.009) and those using stimulants (*M*diff = 0.61, *SD* = 0.21, $p$ = 0.017). Additionally, patients using opioids performed worse on memory than those using cannabis, which was marginally significant (*M*diff = 0.96, *SD* = 0.35, $p$ = 0.051). A significant main effect was found for executive functioning, with no significant post–hoc differences between substances.

***Table 4.1.*** Patient characteristics in the total sample and per primary–problem substance. Post–hoc gives a description of significant differences.

| | Total | Alcohol (A) | Cannabis (C) |
|---|---|---|---|
| | (*n* = 656) | (*n* = 391) | (*n* = 123) |
| Mean age in years (*SD*) | 40.4 (13.9) | 46.6 (12.6) | 28.9 (8.9) |
| Sex (%) | | | |
| male | 505 (77) | 285 (73) | 105 (85) |
| female | 151 (33) | 106 (27) | 18 (15) |
| Health care centre (%) | | | |
| IrisZorg | 178 (27) | 102 (26) | 32 (26) |
| Novadic–Kentron | 166 (25) | 96 (25) | 30 (24) |
| Tactus | 141 (22) | 97 (25) | 20 (16) |
| Vincent van Gogh | 171 (26) | 96 (25) | 41 (33) |
| Level of education (%) | | | |
| low | 126 (19) | 64 (16) | 30 (24) |
| average | 421 (64) | 242 (62) | 78 (63) |
| high | 109 (17) | 85 (23) | 15 (12) |
| Employment (%) | | | |
| employed (full–/part–time) | 253 (39) | 148 (38) | 47 (38) |
| unemployed | 229 (35) | 112 (29) | 51 (42) |
| incapacitated | 139 (21) | 96 (25) | 25 (20) |
| retired | 35 (5) | 35 (9) | 0 (0) |
| Marital status (%) | | | |
| single | 269 (41) | 118 (30) | 76 (62) |
| with partner | 256 (39) | 168 (43) | 37 (30) |
| separated/divorced | 119 (18) | 95 (24) | 10 (8) |
| widowed | 12 (2) | 10 (3) | 0 (0) |
| Years of regular use* | (*n* = 381) | (*n* = 229) | (*n* = 65) |
| mean no. years (*SD*) | 14.01 (11.54) | 15.78 (12.93) | 13.26 (8.33) |
| Polysubstance use* (%) | (*n* = 432) | (*n* = 247) | (*n* = 71) |
| no | 133 (31) | 125 (51) | 5 (7) |
| yes | 299 (69) | 122 (49) | 66 (93) |
| Abstinence** (%) | | | |
| no (< 7 days) | 474 (72) | 275 (70) | 107 (87) |
| yes (7–41 days) | 128 (20) | 83 (21) | 8 (7) |
| yes (≥ 42 days) | 54 (8) | 33 (8) | 8 (7) |

| | Stimulants (S) | Opioids (O) | *p*–value | Post–hoc |
|---|---|---|---|---|
| | (*n* = 100) | (*n* = 26) | | |
| | 30.2 (8.8) | 43.0 (9.9) | < 0.01 | A, O > C, S |
| | | | < 0.01 | |
| | 80 (80) | 25 (96) | | |
| | 20 (20) | 1 (4) | | |
| | | | < 0.01 | |
| | 21 (21) | 21 (81) | | |
| | 29 (29) | 3 (12) | | |
| | 20 (20) | 1 (4) | | |
| | 30 (30) | 1 (4) | | |
| | | | < 0.01 | |
| | 18 (18) | 11 (42) | | |
| | 76 (76) | 14 (54) | | |
| | 6 (6) | 1 (4) | | |
| | | | < 0.01 | |
| | 44 (44) | 8 (31) | | |
| | 45 (45) | 14 (54) | | |
| | 11 (11) | 4 (15) | | |
| | 0 (0) | 0 (0) | | |
| | | | < 0.01 | |
| | 54 (54) | 14 (54) | | |
| | 35 (35) | 7 (27) | | |
| | 10 (10) | 4 (15) | | |
| | 1 (1) | 1 (4) | | |
| | (*n* = 60) | (*n* = 17) | | |
| | 8.90 (6.43) | 14.29 (12.25) | < 0.01 | A, C > S |
| | (*n* = 76) | (*n* = 23) | < 0.01 | |
| | 1 (1) | 0 (0) | | |
| | 75 (99) | 23 (100) | | |
| | | | < 0.01 | |
| | 56 (56) | 25 (96) | | |
| | 35 (35) | 0 (0) | | |
| | 9 (9) | 1 (4) | | |

***Table 4.1.*** Continued.

| | Total | Alcohol (A) | Cannabis (C) |
|---|---|---|---|
| | (*n* = 656) | (*n* = 391) | (*n* = 123) |
| Abstinence duration* | (*n* = 182) | (*n* = 116) | (*n* = 16) |
| mean no. days (*SD*) | 42.85 (57.50) | 36.84 (42.80) | 66.44 (88.52) |
| History of treatment* (%) | (*n* = 650) | (*n* = 387) | (*n* = 122) |
| no | 357 (55) | 210 (54) | 86 (71) |
| yes | 293 (45) | 177 (46) | 36 (30) |
| CIDI–SAD* (*SD*) | (*n* = 470) | (*n* = 287) | (*n* = 81) |
| dependence | 4.79 (1.75) | 4.71 (1.77) | 4.68 (1.77) |
| abuse | 2.09 (1.11) | 2.05 (1.11) | 1.94 (1.04) |
| severity | 6.11 (2.21) | 6.00 (2.20) | 6.00 (2.34) |
| DASS–21* (*SD*) | (*n* = 581) | (*n* = 353) | (*n* = 107) |
| depression | 13.89 (11.29) | 13.47 (11.40) | 15.87 (10.89) |
| anxiety | 9.52 (8.43) | 8.96 (7.87) | 11.03 (9.43) |
| stress | 15.61 (10.27) | 14.14 (9.63) | 18.92 (9.96) |
| DASS–21 total | 39.05 (26.53) | 36.57 (25.78) | 45.81 (26.29) |

Note: patients with sedatives or gamma–hydroxybutyrate (GHB) as the primary–problem substance are only included in the total sample and not separately described; CIDI–SAD = Section Alcohol & Drugs of the Composite International Diagnostic Interview; DASS–21 = Depression Anxiety Stress Scales; * = Due to missing data the *n* included is mentioned separately; ** = Abstinence was only assessed for the primary–problem substance.

| | Stimulants (S) | Opioids (O) | *p*–value | Post–hoc |
|---|---|---|---|---|
| | (*n* = 100) | (*n* = 26) | | |
| | (*n* = 44) | (*n* = 1) | | |
| | 46.00 (68.84) | 270.00 (–) | < 0.01 | |
| | (*n* = 100) | (*n* = 25) | < 0.01 | |
| | 48 (48) | 5 (20) | | |
| | 52 (52) | 20 (80) | | |
| | (*n* = 69) | (*n* = 20) | | |
| | 5.42 (1.34) | 4.30 (2.03) | < 0.01 | A, C < S |
| | 2.48 (1.02) | 1.80 (1.36) | < 0.01 | A, C < S |
| | 6.99 (1.74) | 5.40 (2.80) | < 0.01 | A, C < S |
| | (*n* = 83) | (*n* = 24) | | |
| | 14.00 (11.50) | 10.42 (10.04) | 0.11 | |
| | 9.78 (8.88) | 8.25 (8.43) | 0.13 | |
| | 18.07 (11.24) | 12.08 (11.18) | < 0.01 | A, O < C; A < S |
| | 42.10 (27.45) | 30.75 (26.45) | < 0.01 | A < C |

***Table 4.2.*** Mean (*SD*) Montreal Cognitive Assessment (MoCA) domain (MoCA–DS) and total scores (MoCA–TS) for the total sample and per primary–problem substance. Post–hoc gives a description of significant differences.

| MoCA–DS (score range) | Total (*n* = 656) | Alcohol (A) (*n* = 391) | Cannabis (C) (*n* = 123) |
|---|---|---|---|
| Executive functioning (0–2) | 1.31 (0.67) | 1.27 (0.68) | 1.45 (0.66) |
| Visuospatial abilities (0–4) | 2.77 (0.94) | 2.73 (0.95) | 2.91 (0.90) |
| Attention (0–6) | 5.40 (0.97) | 5.44 (0.95) | 5.42 (0.92) |
| Language (0–5) | 4.46 (0.72) | 4.44 (0.76) | 4.48 (0.67) |
| Abstract reasoning (0–2) | 1.52 (0.63) | 1.51 (0.64) | 1.58 (0.60) |
| Memory (0–5) | 3.30 (1.49) | 3.21 (1.56) | 3.65 (1.24) |
| Orientation (0–6) | 5.75 (0.61) | 5.76 (0.62) | 5.74 (0.54) |
| MoCA– TS (0–30) | 25.52 (3.12) | 25.30 (3.23) | 26.33 (2.69) |
| *n* (%) scoring < 25 | 206 (31) | 134 (34) | 26 (21) |

Note: patients with sedatives or gamma–hydroxybutyrate (GHB) as the primary–problem substance are only included in the total sample and not separately described.

### *Factors related to cognitive performance*

In the total sample, the MoCA–TS was negatively correlated with age ($r$ = −0.28, $p$ < 0.001), with a shared variance of only 9%. None of the other investigated factors (i.e. years of regular use, abstinence duration, severity of dependence and/or abuse, depression, anxiety and stress) were significantly correlated with the MoCA–TS. Abstinence and polysubstance use were also not related to the MoCA–TS (all $p$–values > 0.05). Since age was significantly correlated with MoCA–TS in the total sample and there was a significant difference in mean age between substances, the correlation between MoCA–TS and age was calculated per primary–problem substance. For alcohol age was negatively correlated with MoCA–TS ($\rho$ = −0.331, $p$ < .001), for cannabis this negative correlation was marginally significant ($\rho$ = −0.148, $p$ = .051), for stimulants age was positively correlated with MoCA–TS ($\rho$ = 0.173, $p$ = .042), and the correlation between age and MoCA–TS for opioids was negative but not significant ($r$ = −0.195, $p$ = .170).

| | Stimulants (S) ($n$ = 100) | Opioids (O) ($n$ = 26) | $p$–value | Post–hoc |
|---|---|---|---|---|
| | 1.34 (0.66) | 1.12 (0.77) | 0.04 | |
| | 2.88 (0.88) | 2.27 (1.00) | < 0.01 | C, S > O |
| | 5.40 (0.90) | 5.23 (1.31) | 0.74 | |
| | 4.51 (0.70) | 4.58 (0.64) | 0.68 | |
| | 1.51 (0.58) | 1.65 (0.63) | 0.55 | |
| | 3.33 (1.33) | 2.69 (1.72) | 0.01 | A < C |
| | 5.79 (0.54) | 5.77 (0.65) | 0.94 | |
| | 25.86 (2.72) | 24.69 (3.88) | < 0.01 | A < C |
| | 27 (27) | 10 (38) | 0.03 | A > C |

# Discussion

To our knowledge this is the first study in addiction care in which a large and heterogeneous group of patients with SUD are assessed on cognitive impairments. The current study found a prevalence of cognitive impairments of 31% in the total sample, ranging from 21% for cannabis to 39% for opioids. Patients using alcohol had a significantly lower MoCA–TS than those using cannabis and it was found that in the total sample younger patients scored significantly higher than older patients. Years of regular use, abstinence (duration), severity of dependence and/or abuse, polysubstance use, depression, anxiety and stress were not related to MoCA outcomes.

Previous research shows a prevalence of cognitive impairments in patients with SUD ranging from 30% – 80% (Copersino et al., 2009). The prevalence in our study falls at the bottom of this range, yet is still remarkable as cognitive impairments are found to affect treatment outcomes. Differences between primary–problem substances on MoCA performance were not as profound as expected. Patients using alcohol had lower outcomes than those using cannabis, both on the MoCA–TS and on MoCA–DS memory, and patients using opioids had lower outcomes on visuospatial abilities in comparison to those using cannabis and stimulants. The lack of significant differences could be influenced by the high percentage of polysubstance users in our sample and the relatively small number of patients using opioids (see Table 4.1). There was a significant difference in age between substance types, and age was found to have an effect on MoCA performance in this study. The finding that age is negatively correlated to MoCA scores is in line with findings in a sample of patients with AUD aged > 18 (Alarcon et al., 2015) and also in a sample of healthy controls aged 25–91 (Freitas et al., 2012). It is, however, striking that the directionality of the correlation between age and MoCA–TS was different for stimulants than for the other substances. This may be a consequence of the primarily enhancing effects of stimulant intoxication at low doses (Scott et al., 2007; Spronk et al., 2013), although abstinence was no significant factor on MoCA performance in the total sample. Substance type and age are thus factors that should be taken into account when interpreting the MoCA–TS.

SUD patients may experience more psychological complaints than healthy people, and they are not always abstinent at intake. In our sample, none of the variables (abstinence, abstinence duration, polysubstance use, years of regular use, severity of dependence and/or abuse, depression, anxiety and stress) were related to MoCA outcome. The lack of relations between MoCA–TS and depression, anxiety and stress is in line with recent findings in a sample of polysubstance users where the MoCA–TS was not related to results on a (psychiatric) symptom checklist (Hagen et al., 2019). As for abstinence and abstinence duration, our findings are not in line with the literature, as a review by Walvoort et al. (2013) points to a minimum period of six weeks abstinence before an extensive (neuro)psychological assessment can be carried out validly.

In clinical practice, cognitive impairments often remain undetected at the start of or during treatment. Early detection of cognitive impairments is essential to increase the chance of a favourable outcome of treatments and the MoCA is a relatively quick and easy tool to assess cognitive functioning at intake. When cognitive impairments are indeed present, adequate interventions, such as cognitive training (Reijnders et al., 2013) or errorless learning (Rensen et al., 2019) may help to increase treatment compliance, self–efficacy and cognitive performance. As our results show, screenings for cognitive impairment can be validly interpreted in every patient applying for addiction treatment, independent of possibly relevant characteristics. When interpreting findings obtained with the MoCA one should, however, take into account that older adults with SUD may perform lower than younger adults with SUD (except for stimulants, where the opposite effect of age was found).

Some strengths to our study are in the design, which was kept as close to clinical practice as possible, by only adding a MoCA assessment to the intake procedure as usual. Also, patients were only excluded if administration of the MoCA was impossible. Consequently, a large number of patients using different substances, whether or not abstinent and with a variety of psychological complaints, could be included. Therefore, results are representative of clinical practice. There are some limitations to the current study. First, it was impossible to perfectly balance the number of patients for each primary–problem substance. Users of cocaine, amphetamines and ecstasy were therefore combined into 'stimulants' and the relatively small number of patients using opioids lowered the power of the analyses that included this group. The small number of patients using sedatives and GHB were not included in the comparisons making it impossible to conclude about consequences on cognitive functioning for these substances. Finally, the rather low sensitivity and specificity of the MoCA for use in addiction care (Bruijnen, Jansen, et al., 2019) may have influenced our results and therefore the actual prevalence of cognitive impairments may well be different than that currently found

In conclusion, a prevalence of 31% for cognitive impairments was found in addiction care and, therefore, detection of cognitive impairments at an early stage of treatment is important to determine the course of treatment and maximise treatment outcome. Significant differences in MoCA performance were only found between patients using alcohol and cannabis, but not between other substances. Because of the underrepresentation of patients using opioids in our sample, differences between this group and the other substance groups cannot be excluded. More research is needed on how to adjust for the effect of age on MoCA performance in individuals without SUD. Finally, we emphasise the fact that the MoCA is not intended as a diagnostic instrument and that a full neuropsychological assessment is always preferred. We therefore recommend to use the MoCA as a first screen in the triage for subsequent more expensive and time–consuming (extensive neuropsychological) assessments.

Inmiddels werk ik bijna een jaar bij de Mutsaersstichting, waar ik mij opnieuw voel als die stagiaire die (vrijwel) niets weet. Pieke, allereerst wil ik jou bedanken dat je mij deze kans hebt gegeven om eindelijk het kind– en jeugddomein te verkennen, dat je potentie in mij zag (waar ik het af en toe kwijt lijk te zijn). Ik hoop als dit achter de rug is, die potentie waar te kunnen maken.

Daarnaast heb ik vele nieuwe collega's leren kennen, bij enkelen daarvan voelt het alsof ik jullie al jaren ken, Elke en Ellis (ja, jou ken ik inderdaad nog van de komkommers twintig jaar geleden): we begonnen op dezelfde dag en het klikte onmiddellijk! Wat fijn dat ik bij jullie mezelf kan zijn, onbezonnen kletsen, lachen, gieren en brullen. Wie weet wat de toekomst voor ons brengt.

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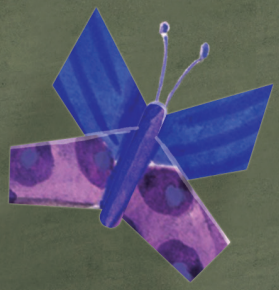

# Chapter 5

## The course of cognitive performance during inpatient treatment in patients with alcohol use disorder (AUD) with no, mild, or major neurocognitive disorders (NCD)

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## Abstract

In patients with a history of chronic alcohol abuse, neurocognitive disorders (NCD) are not uncommon. The current study aimed to explore the course of cognitive performance, as measured by the Montreal Cognitive Assessment (MoCA), and everyday cognitive functioning, as measured by the Patient Competency Rating Scale (PCRS), in a large group of patients with alcohol use disorder (AUD) admitted to the Centre of Excellence for Korsakov and Alcohol–related Cognitive Impairments. A multiple time–series design was used, in which the MoCA was administered at three time points of assessment, and the PCRS was completed by both the patient and a clinician at two time points, all during clinical treatment. A total of 524 patients were included, 71 of whom were diagnosed with AUD only, 284 with AUD and mild NCD (ARCI), and 169 with AUD, major NCD and fulfilling criteria for Korsakoff's syndrome (KS). Cognitive performance improved for all three groups during treatment, sustained abstinence, and recovery from AUD. A low memory performance on the MoCA without improvement over time was predictive for KS, while improvement on this domain did not differentiate between AUD and ARCI. Changes in overall cognitive performance and orientation in patients with KS were positively related to changes in everyday cognitive functioning.

# Introduction

About 30% – 80% of the people seeking treatment for alcohol use disorder (AUD) have cognitive impairments (Copersino et al., 2009; Bruijnen, Dijkstra, et al., 2019). In patients with Korsakoff's syndrome (KS) cognitive impairments are severe and a hallmark of the disorder. KS in chronic alcoholics is caused by thiamine deficiency, which is an indirect effect of the chronic alcohol use (Arts et al., 2017). Its symptoms include severe memory deficits, confabulations, apathy, disorders of affect, social–cognitive problems and impaired insight into the illness (Arts et al., 2017; Rensen et al., 2017). However, most patients with alcohol–related cognitive impairments (ARCI; Heirene et al., 2018) do not fulfil the criteria for KS, as they have less severe cognitive deficits, which are often overlooked and underdiagnosed by clinicians. ARCI may be the result of indirect effects of alcohol use, such as liver cirrhosis or cerebrovascular risk factors, but may also be caused by direct effects of long–term alcohol abuse in individuals who are not (or not long) abstinent from alcohol, like the toxic actions of alcohol itself or the consequences of alcohol withdrawal. Acute alcohol intoxication primarily acts upon executive functions such as planning, verbal fluency, memory and complex motor control (Peterson et al., 1990; Lyvers et al., 2010). However, both residual and chronic symptoms of alcohol intoxication are diffuse and found in all cognitive domains (Stavro et al., 2013).

Patients with ARCI themselves do not always report subjective complaints because these may be obscured by the addiction itself, or because of a lack of insight into their own cognitive deficits (Walvoort et al., 2016). In general, the absence of subjective experiences of cognitive deficits is a poor predictor of cognitive performance on objective measures (Horner et al., 1999). In order to detect cognitive impairments in individuals with AUD, cognitive screens can be used that quantify cognitive performance. A relatively short and easy to administer screener is the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The MoCA is often used for the detection of ARCI at an early stage of addiction treatment (Bruijnen, Jansen, et al., 2019) and is being implemented in addiction care more and more (Copersino et al., 2009; Alarcon et al., 2015; Ewert et al., 2018; Ridley et al., 2018). Oudman et al. (2014) found the MoCA to be superior to the Mini–Mental State Examination (Folstein et al., 1975) in distinguishing patients with KS from controls. The availability of three alternate forms of the MoCA makes it possible to retest individuals over time (Chertkow et al., 2011) and thus follow the course of cognitive functioning during treatment. All three versions are found to be largely equivalent and the MoCA total score is a reliable measure for screening cognitive performance (Bruijnen et al., 2020).

The first aim of the present study was to explore the course of cognitive performance on the MoCA during treatment towards abstinence and recovery in three patient groups with AUD: patients with AUD without cognitive impairments, patients with ARCI (but no KS), and patients with KS. It was hypothesised that patients with AUD–only showed the highest overall cognitive performance, followed by patients with ARCI and those with KS respectively. Furthermore, we expected that between clinical admission, when abstinence is not always guaranteed, and after six weeks of admission, all three groups would show an improved cognitive performance, where patients with AUD–only were hypothesized to have a near–ceiling score on the MoCA. Between six weeks of admission and clinical discharge, patients with ARCI were expected to have improved further, while cognitive performance in patients with AUD–only and KS was expected to have stayed relatively stable.

The second aim was to explore the course of everyday cognitive functioning in patients with AUD–only, ARCI or KS, as measured with the Patient Competency Rating Scale (PCRS; Prigatano et al., 1986). The PCRS is a rating scale that can be completed by both the patient and a clinician who is familiar with the patient and his/her abilities. The PCRS primarily aims to evaluate an individual's awareness of cognitive, self–care, and social deficits. The possibility to have the questionnaire assessed by both the patient and a clinician makes it possible to map everyday cognitive functioning during treatment from a clinical viewpoint. Everyday cognitive functioning was hypothesized to be best for patients with AUD–only, followed by patients with ARCI and those with KS respectively. Furthermore, it was hypothesized that everyday cognitive functioning was better at clinical discharge than at six weeks of admission in patients with AUD–only and those with ARCI, according to both the patient and the clinician. The reported improvement was expected to be greater according to the clinician than according to the patient.

The third aim was to determine if changes in cognitive performance (MoCA) were related to changes in everyday cognitive functioning (PCRS), between the sixth week of admission and clinical discharge. It was hypothesized that these changes were positively correlated and that the correlations were highest for the clinician ratings.

# Methods

### *Design*

A multiple time–series design was used, in which the MoCA was administered at three time points of assessment during clinical treatment. The first administration took place at intake or clinical admission (T0). The second administration followed after approximately six weeks of admission (T1). The third and final administration was right before clinical discharge (T2). Data were collected between May 2010 and May 2019 and supplemented from an existing clinical research database. The study was approved by the internal review board of Vincent van Gogh Institute for Psychiatry and all patients provided informed consent in accordance with the Dutch General Data Protection Regulation and the declaration of Helsinki.

### *Participants*

All participants were inpatients of the Centre of Excellence for Korsakoff and Alcohol–Related Cognitive Impairments of Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. They were referred to the clinic with suspected cognitive impairments related to long–term alcohol use. The patients were diagnosed by a multidisciplinary team in the first 10 to 12 weeks of admission, based on an extensive neuropsychological assessment that was administered after a minimum of six weeks abstinence (Walvoort et al., 2013), a neurological and psychiatric examination, observations from therapists and (psychiatric) nurses, physical exams, and neuroradiological examination (MRI). Note that the MoCA was not used in this diagnostic process.

Three patient groups were included in the study, all of whom fulfilled the DSM–5 criteria for AUD, with two groups also fulfilling the DSM–5 criteria for mild and major substance–induced (alcohol) neurocognitive disorder (NCD; APA, 2013). The first group was diagnosed with AUD (not fulfilling the criteria for NCD), the second group with ARCI (fulfilling the criteria for mild NCD) and the third group with KS (fulfilling the criteria for major NCD). The latter group also fulfilled the clinical criteria of KS described by Kopelman (2002) and Arts et al. (2017). These include 1) the presence of a persistent memory impairment resulting in severe deficits in social functioning, 2) the absence of delirium or dementia due to a neurodegenerative disease, 3) evidence for a history of Wernicke encephalopathy, 4) confabulatory behaviour, and 5) a history of malnutrition or thiamine deficiency. None of the patients had any evidence of brain abnormalities that could account for their condition apart from atrophy or white–matter lesions associated with chronic alcohol use (Arts et al., 2017), and none of the patients fulfilled the proposed criteria for alcohol–related dementia (Oslin et al., 1998). Finally, none of the included patients had hearing problems, language or communication deficits, or visual deficits that made MoCA administration impossible.

The Centre of Excellence for Korsakoff and Alcohol–Related Cognitive Impairments consist of two separate treatment wards for patients with either ARCI or KS. As patients with AUD–only have no cognitive impairments (after having completed neuropsychological assessment), they are discharged or referred to outpatient aftercare soon after completing the diagnostic process. For the other two groups (ARCI and KS), treatment focuses on reaching the highest level of autonomy in activities of daily living. When treatment is completed, they are also discharged, in most cases to their homes with outpatient aftercare (mostly patients with ARCI), or placed in a long–term residence or sheltered living facility (mostly patients with KS). As these long–term aftercare options have a limited capacity and often have waiting lists, this contributes to a longer stay duration in the patient group who cannot return home.

***Materials***

*Montreal Cognitive Assessment*

The MoCA (Nasreddine et al., 2005) consists of 12 items. Scores on all items add up to the MoCA Total Score (MoCA–TS) with a maximum of 30 points, where a higher score represents better cognitive performance. An adjustment for level of education is applied in which participants with a low level of education are awarded two extra points and participants with an average level of education are awarded one extra point, maintaining the maximum score of 30 (Bruijnen, Jansen, et al., 2019).

Seven Domain Scores (MoCA–DS) were calculated: executive functioning (alternating trail making and verbal fluency; 0–2 points), visuospatial abilities (figure copy and clock drawing; 0–4 points), attention, concentration and working memory (digit span, sustained attention and serial subtraction; 0–6 points), language (animal naming and sentence repetition; 0–5 points), abstract reasoning (0–2 points), memory (0–5 points) and orientation (0–6 points).

Finally, the Memory Index Score (MoCA–MIS) was calculated separately, in which freely recalled words receive three points, words recalled after a category cue receive two points (cued recall), and correct identification after a multiple–choice cue (recognition) receives one point, with a maximum of 15 points (Julayanont et al., 2014).

All three authorized and validated parallel versions of the Dutch MoCA were used in this study (Costa et al., 2012; Nasreddine et al., 2016; Bruijnen et al., 2020). Administration of the MoCA takes approximately 15 minutes and scoring can mostly be done during administration.

*Patient Competency Rating Scale*

The PCRS was developed to evaluate an individual's awareness of cognitive, self–care, and social deficits after (traumatic) brain injury (Prigatano et al., 1986). The scale must be administered to the patient and an informant (clinician and/or relative) who is familiar with the patient and his/her abilities. The PCRS contains 30 items in which the respondent is asked to judge how easy or difficult it is (for the patient) to perform a variety of tasks. Each item is rated on a 5–point Likert scale, ranging from 1 ('cannot do') to 5 ('can do with ease'). A total score (PCRS–TS) ranging from 30 to 150 can be obtained, where higher scores represent a higher level of everyday cognitive functioning (Kolakowsky–Hayner et al., 2012). Four domain scores were calculated, measuring activities of daily living (PCRS–ADL; scoring range 8–40), cognitive abilities (PCRS–CO; scoring range 8–40), interpersonal abilities (PCRS–IP; scoring range 7–35) and emotional lability (PCRS–EM; scoring range 7–35; Leathem et al., 1998). The PCRS has a good internal consistency (Cronbach α = 0.87–0.89) and test–retest reliability for all scores range from 0.63 to 0.84, as measured in patients with acquired brain injury (Hellebrekers et al., 2017).

***Procedure***

Each patient that was referred to the clinic was discussed in a multidisciplinary team to determine if there was a positive indication for clinical admission. As part of the intake procedure, MoCA 7.1 was administered to each patient at intake or preferably in the first week of admission (T0). In the sixth week of admission, one of the psychologists made an appointment with the patient for administration of MoCA 7.2 (T1). Note that the time between intake and clinical admission varied between patients. Therefore, the time between T0 and T1 also varies, namely between 16 and 395 days ($M$ = 62.7, $SD$ = 45.6; see Figure 5.1, left panel). When the patient was (soon to be) clinically discharged, another appointment was made for the administration of MoCA 7.3 (T2). The time between T1 and T2 varied based on the duration of clinical admission, namely between 5 and 645 days ($M$ = 124.2, $SD$ = 93.0; see Figure 5.1, right panel). The PCRS was completed by the patient at both T1 and T2, and by the primary responsible caregiver of the patient preferably in the same week. Both the MoCA and the PCRS were part of care as usual and were included in the Routine Outcome Monitoring (ROM), among several other questionnaires that are not part of the current study. Relevant demographic information was derived from the electronic patient files.

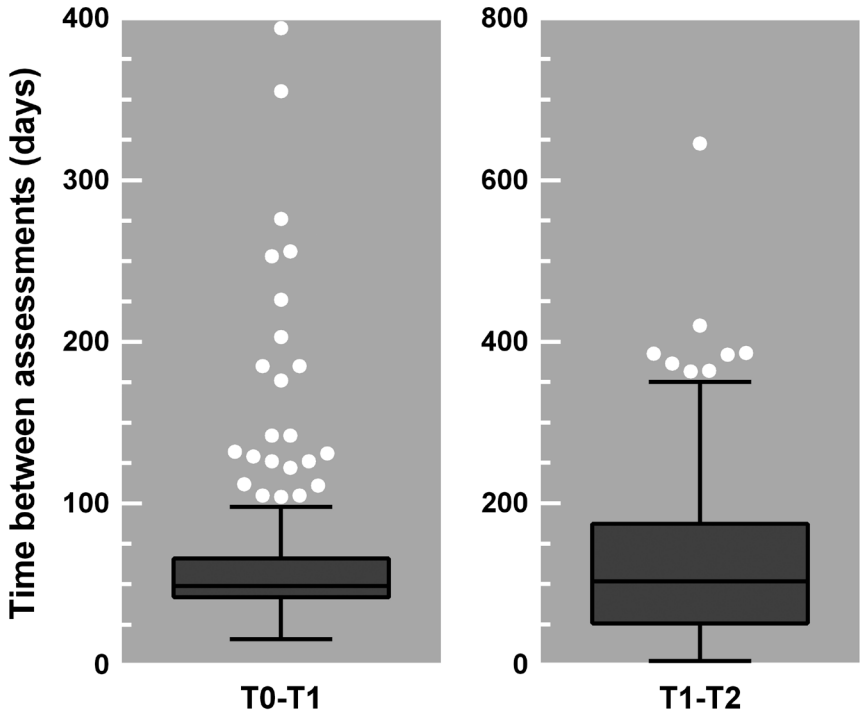



***Figure 5.1.*** Tukey box–and–whisker plots showing the distribution of the time between two assessments in days. The time between T0 (intake or clinical admission) and T1 (after 6 weeks of clinical admission) ranged from 16 to 394 days (left panel), and the time between T1 (after 6 weeks of clinical admission) and T2 (clinical discharge) ranged from 5 to 645 days (right panel). The box plots indicate the interquartile range and median; the whiskers indicate the minimum and maximum values, excluding the outliers which are represented by the white circles.

***Analyses***

The first author thoroughly checked all scores of the MoCA and corrected scoring errors of the assessor when needed. Ambiguities in the scoring for which the instructions on www.mocatest.org were not fully specified were scored or corrected in a consistent manner according to strict criteria (similar to the instructions for the newly released MoCA version 8.1 which was not yet available in Dutch at the time of data collection). The procedure of checking scores of all items by the same assessor eliminated inter–rater differences that were previously found to influence results (Cumming et al., 2020).

First, characteristics of the patient sample as a whole are presented, as well as for all three groups. Differences in patient characteristics between groups were explored using univariate ANOVAs for scaled variables and chi–square tests for categorical variables.

Second, to explore cognitive performance over the course of treatment, a mixed model ANOVA was used with group (AUD, ARCI and KS) as the between–subject factor and time (T0, T1 and T2) as the within–subject factor. The analysis was run for MoCA–TS, each MoCA–DS and MoCA–MIS, to explore in detail if there are certain domains on which performance changes more than others over the course of treatment.

Third, to explore everyday cognitive functioning over the course of treatment, a mixed–model ANOVA was used with group (AUD, ARCI and KS) as the between–subject factor and time (T1 and T2) as the within–subject factor, ran separately for the patient and clinician ratings. The analyses were run for PCRS–TS and each PCRS–DS, to explore in detail if there are certain domains on which everyday cognitive functioning changes more than others over the course of treatment.

Finally, to explore if changes in cognitive performance were related to changes in everyday cognitive functioning, change scores were calculated between T1 and T2 for all scores (MoCA–TS, all MoCA–DS, MoCA–MIS, PCRS–TS, and all PCRS–DS; patient and clinician ratings). Pearson correlations were calculated between the MoCA change scores and the PCRS change scores.

Alpha was set at 0.05 for all main analyses, but to adjust for the Type 1 error rate, Bonferroni corrected, Hochberg's GT2 (unequal sample sizes) or Games–Howell (non–homogeneous population variances) post–hoc tests were used when appropriate. Also, the effect sizes ($\eta^2$) were calculated and reported based on Lakens (2013). All analyses were performed using IBM SPSS version 25.0.

# Results

### *Patient characteristics*

Between June 2010 and March 2019, 796 cases were admitted to the clinic (600 unique patients, as some were readmitted over the years). Of these unique patients, 73.8% were men. The age at admission ranged from 27–86 years, with a mean of 56.6 years (*SD* = 8.7). Of all 796 cases, 91 (11.4%) were diagnosed with AUD, 415 (52.1%) with ARCI and 210 (26.4%) with KS. In the remaining 80 cases ('other'; 10.1%), 57 were undiagnosed for various reasons, mostly due to leaving the clinic early against medical advice, and another 23 patients had a diagnosis other than AUD, ARCI or KS (i.e. a neurodegenerative disorder [*n* = 10], non–alcohol or polysubstance use disorder [*n* = 5], NCD not due to a substance [*n* = 4], psychotic disorder [*n* = 2] and depression [*n* = 2]). Comparisons between these four groups revealed no significant differences for sex distribution, level of education (classified as described by Bruijnen, Jansen, et al., 2019) and abstinence duration at MoCA administration. We found that patients with KS were significantly older than both patients with AUD and those with ARCI. Duration of admission was shortest for the 'other' patients, followed by patients with AUD, ARCI and KS, respectively. Patients with ARCI were significantly more often readmitted to this clinic than all other patient groups (Table 5.1).

Furthermore, in 232 of all 796 cases the MoCA was not administered, most probably accounted for by: 1) no diagnosis or a diagnosis other than AUD, ARCI or KS ; 2) MoCA administration being limited to version 7.1 in the first two years of data collection and not being immediately implemented in treatment as usual by all professionals (assessment of MoCA versions 7.2 and 7.3 was introduced in March 2012 and July 2013, respectively); 3) patients being readmitted to the clinic did not complete the MoCA again if they already completed all three versions in their previous admission, 4) patients not being motivated to complete the MoCA assessment; and 5) inability to administer the MoCA due to physical limitations or insufficient Dutch language skills.

In the following analyses, only patients with a diagnosis of AUD, ARCI or KS, and at least one MoCA administration were included, to comprise our total sample of 524 patients. Of these, 71 were diagnosed with AUD, 284 with ARCI and 169 with KS. The other 272 patients were excluded. To rule out possible selection bias between the included and excluded cases in terms of demographic characteristics and severity of cognitive impairments, they were statistically compared to the included patients. The distribution of patients between diagnostic groups was unequal, where proportionately more patients with ARCI were excluded, while proportionately more patients with KS were included ($\chi^2(2, n = 716) = 11.55$, $p = .003$). There were no differences in age, sex,

level of education, and abstinence duration at MoCA administration (all *p*–values > 0.05). As expected based on the abovementioned reasons for exclusion, the excluded cases had a significant shorter admission duration than the included cases (*M*diff = −78.15, $t(775) = -9.33$, $p < .001$) and significantly more readmissions to the clinic (*M*diff = 0.67, $t(323.60) = 7.50$, $p < .001$).

***Course of cognitive performance***

There was a significant main effect of time on overall cognitive performance (MoCA–TS; $F(1.86, 303.83) = 23.39$, $p < .001$, $\eta^2 = 0.124$) and contrasts revealed that this was a significant linear improvement ($F(1, 163) = 40.25$, $p < .001$). There was also a significant main effect of group on cognitive performance ($F(2, 163) = 34.91$, $p < .001$, $\eta^2 = 0.300$) and post–hoc tests showed that differences between all three groups were significant. Patients with AUD scored higher than those with ARCI (*M*diff = 2.55, *SD* = 0.64) and those with KS (*M*diff = 5.72, *SD* = 0.70), and patients with ARCI scored higher than those with KS (*M*diff = 3.18, *SD* = 0.57; all *p*–values < .001). The interaction effect between time and group was not significant ($F(3.73, 303.83) = 1.03$, $p = .390$, $\eta^2 = 0.011$; see Figure 5.2, left top panel).

Significant main effects of time were found for all seven domains (MoCA–DS): executive functioning ($F(2, 326) = 29.88$, $\eta^2 = 0.154$), visuospatial abilities ($F(2, 326) = 12.65$, $\eta^2 = 0.071$), attention ($F(1.88, 306.21) = 5.53$, $\eta^2 = 0.033$), language ($F(1.86, 303.34) = 46.71$, $\eta^2 = 0.221$), abstract reasoning ($F(1.89, 308.70) = 23.00$, $\eta^2 = 0.123$), memory ($F(1.89, 307.78) = 7.94$, $\eta^2 = 0.044$) and orientation ($F(1.70, 277.71) = 14.17$, $\eta^2 = 0.078$; all *p*–values ≤ .005). The main effect of group on cognitive performance was significant for the domains executive functioning ($F(2, 163) = 3.83$, $p = .024$, $\eta^2 = 0.045$), memory ($F(2, 163) = 68.62$, $p < .001$, $\eta^2 = 0.457$) and orientation ($F(2, 163) = 95.43$, $p < .001$, $\eta^2 = 0.539$). As the direction of the effects differed between domains, Table 5.2 provides an outline of significant contrasts and post–hoc differences.

***Table 5.1.*** Patient characteristics, means and standard deviations (*SD*) for the total sample and split per group. Post–hoc gives a description of the direction of significant differences between groups.

| | Total | AUD | ARCI |
|---|---|---|---|
| | (*n* = 796) | (*n* = 91) | (*n* = 415) |
| Mean age in years (*SD*) | 56.63 (8.71) | 54.26 (10.00) | 55.98 (8.22) |
| range | 27 – 86 | 27 – 76 | 29 – 78 |
| Sex (%)[a] | | | |
| male | 443 (73.8) | 53 (71.6) | 194 (71.1) |
| female | 157 (26.2) | 21 (28.4) | 79 (28.9) |
| Level of education (%)[b] | | | |
| unknown | 54 (6.8) | 3 (3.3) | 12 (2.9) |
| low | 203 (25.5) | 26 (28.6) | 107 (25.8) |
| average | 417 (52.4) | 42 (46.2) | 238 (57.3) |
| high | 122 (15.3) | 20 (22.0) | 58 (14.0) |
| Mean duration of admission (in days; *SD*) | 147.07 (116.57) | 98.08 (61.33) | 132.84 (101.39) |
| range | 1 – 690 | 1 – 254 | 1 – 611 |
| Mean number of admissions (*SD*) | 1.44 (1.00) | 1.27 (0.68) | 1.68 (1.24) |
| range | 1 – 9 | 1 – 5 | 1 – 9 |
| Mean abstinence duration (in days; *SD*) | | | |
| T0 (*n* = 299) | 77.37 (570.747) | 17.08 (28.78) | 87.11 (748.34) |
| range | 0 – 8897 | 0 – 165 | 0 – 8897 |
| T1 (*n* = 463) | 107.68 (468.14) | 59.08 (40.12) | 106.30 (592.74) |
| range | 0 – 9082 | 5 – 228 | 0 – 9082 |
| T2 (*n* = 313) | 220.04 (541.48) | 123.06 (48.71) | 220.01 (727.17) |
| range | 0 – 9228 | 51 – 324 | 0 – 9228 |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; Other = undiagnosed or a diagnosis other than AUD, ARCI or KS; T0 = baseline/intake; T1 = after six weeks of clinical admission; T2 = at clinical discharge; [a] = only unique patients; [b] = unknown level of education was excluded for group comparisons; * = p < .001; † = Fisher's exact test was used.

| KS | Other | *p*–value | Post–hoc |
|---|---|---|---|
| (*n* = 210) | (*n* = 80) | | |
| 58.65 (7.81) | 57.44 (10.70) | < .001* | KS > AUD, ARCI |
| 37 – 77 | 28 – 86 | | |
| | | .375 | |
| 139 (78.1) | 57 (76.0) | | |
| 39 (21.9) | 18 (24.0) | | |
| | | .226† | |
| 2 (1.0) | 37 (46.3) | | |
| 58 (27.6) | 12 (15.0) | | |
| 110 (52.4) | 27 (33.8) | | |
| 40 (19.0) | 4 (5.0) | | |
| 232.61 (122.53) | 49.67 (82.14) | < .001* | Other < AUD < ARCI < KS |
| 5 – 690 | 0 – 624 | | |
| 1.17 (0.44) | 1.15 (0.64) | < .001* | ARCI > AUD, KS, Other |
| 1 – 4 | 1 – 5 | | |
| | | | |
| 113.82 (460.19) | 8.91 (16.33) | .733 | |
| 0 – 3653 | 0 – 81 | | |
| 139.75 (367.77) | 57.61 (30.53) | .655 | |
| 7 – 3703 | 10 – 140 | | |
| 285.24 (268.98) | 79.43 (84.81) | .317 | |
| 22 – 2408 | 7 – 241 | | |

A significant interaction between time and group on cognitive performance was found for the memory domain ($F(3.78, 307.78) = 3.86$, $p = .005$, $\eta^2 = 0.043$) and contrasts revealed a significant linear improvement ($F(2, 163) = 3.08$, $p = .049$), as well as a significant quadratic trend ($F(2, 163) = 5.10$, $p = .007$) over time. This means that scores for each group did not change equally over time. As can be seen in Figure 5.2, right bottom panel, patients with KS did not change over time and patients with AUD did not change between T1 and T2, while those with ARCI showed linear improvement. Post–hoc tests further revealed that differences between all three groups were significant. Patients with AUD scored higher than patients with ARCI (*M*diff = 1.15, *SD* = 0.24) and those with KS (*M*diff = 2.67, *SD* = 0.22), and patients with ARCI scored higher than those with KS (*M*diff = 1.52, *SD* = 0.16; all *p*–values < .001; see Table 5.2). The interaction between time and group was marginally significant for the orientation domain ($F(3.41, 277.71) = 2.51$, $p = .052$, $\eta^2 = 0.028$), with contrasts revealing a significant linear improvement over time ($F(2, 163) = 3.24$, $p = .042$) and post–hoc tests revealed that differences between all three groups were significant. Patients with AUD scored higher than those with ARCI (*M*diff = 0.37, *SD* = 0.10) and those with KS (*M*diff = 2.20, *SD* = 0.18), and patients with ARCI scored higher than those with KS (*M*diff = 1.83, *SD* = 0.19; all *p*–values ≤ .001; see Table 5.2 and Figure 5.2, left bottom panel).

For MoCA–MIS, significant main effects of both time ($F(1.87, 289.98) = 12.51$, $p < .001$, $\eta^2 = 0.073$) and group ($F(2, 155) = 86.67$, $p < .001$, $\eta^2 = 0.528$) were found, with no significant interaction ($F(3.74, 289.98) = 1.62$, $p = .174$, $\eta^2 = 0.019$). Contrasts revealed a significant linear improvement over time ($F(1, 155) = 14.77$, $p < .001$), as well as a significant quadratic trend ($F(1, 155) = 8.91$, $p = .003$), meaning that not all groups showed the same linear improvement. As can be seen in Figure 5.2, right top panel, patients with KS did not change over time, patients with AUD scored lower on T2 than on T1, while patients with ARCI showed linear improvement. Post–hoc tests further revealed that differences between all three groups were significant. Patients with AUD scored higher than those with ARCI (*M*diff = 2.61, *SD* = 0.48) and those with KS (*M*diff = 6.69, *SD* = 0.47), and patients with ARCI scored higher than those with KS (*M*diff = 4.08, *SD* = 0.40; all *p*–values < .001).

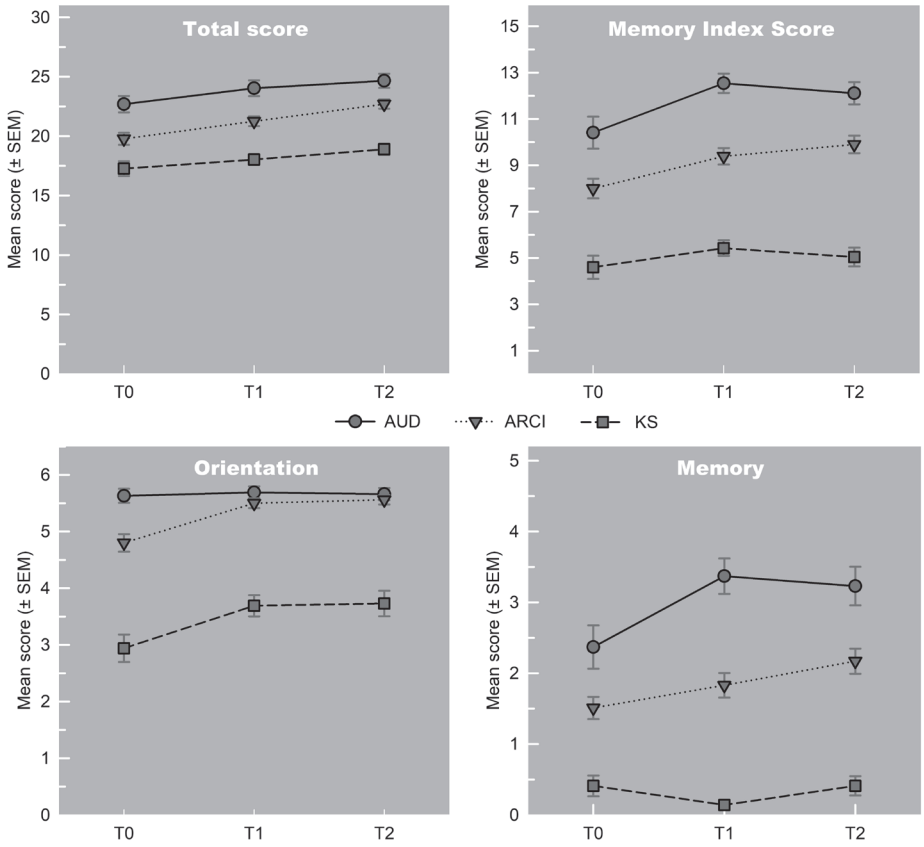



***Figure 5.2.*** Mean Montreal Cognitive Assessment – Total Score (MoCA–TS; top left panel), – Memory Index Score (MoCA–MIS; top right panel), Domain Score orientation (MoCA–DS; bottom left panel), and Domain Score memory (MoCA–DS; bottom right panel) on three assessment time points, split per group.

***Table 5.2.*** Means and standard deviations (*SD*) of the Montreal Cognitive Assessment Domain Scores (MoCA–DS) on all three assessment points for the total sample and split per group. Post–hoc gives a description of the direction of significant differences between groups (column), between assessments (row) and the interaction between groups and assessments (in italics).

| Cognitive domain (range) | Total | AUD |
|---|---|---|
| | (*n* = 166) | (*n* = 35) |
| Executive functioning (0–2) | | |
| T0 | 0.66 (0.69) | 0.77 (0.73) |
| T1 | 1.02 (0.68) | 1.17 (0.71) |
| T2 | 1.18 (0.74) | 1.43 (0.66) |
| *p*–value (post–hoc) | < .001*** (T0 < T1; T0 < T2; T1 < T2††) | |
| Visuospatial abilities (0–4) | | |
| T0 | 1.97 (1.04) | 2.20 (1.05) |
| T1 | 2.39 (1.07) | 2.63 (0.91) |
| T2 | 2.40 (0.98) | 2.74 (0.74) |
| *p*–value (post–hoc) | < .001*** (T0 < T1;T0 < T2††) | |
| Attention (0–6) | | |
| T0 | 5.00 (1.24) | 5.29 (0.99) |
| T1 | 5.17 (1.12) | 5.31 (1.02) |
| T2 | 5.32 (1.01) | 5.51 (0.82) |
| *p*–value (post–hoc) | .005*††† (T0 < T2††) | |
| Language (0–5) | | |
| T0 | 4.07 (0.89) | 4.23 (0.77) |
| T1 | 3.36 (1.01) | 3.51 (1.17) |
| T2 | 3.51 (0.64) | 3.51 (0.66) |
| *p*–value (post–hoc) | < .001***††† (T0 > T1; T0 > T2††) | |
| Abstract reasoning (0–2) | | |
| T0 | 1.15 (0.78) | 1.20 (0.80) |
| T1 | 1.29 (0.75) | 1.37 (0.69) |
| T2 | 1.66 (0.57) | 1.57 (0.66) |
| *p*–value (post–hoc) | < .001***††† (T0 < T2; T1 < T2††) | |
| Memory (0–5) | | |
| T0 | 1.37 (1.57) | 2.37 (1.82) |
| T1 | 1.66 (1.74) | 3.37 (1.48) |
| T2 | 1.87 (1.77) | 3.23 (1.61) |
| *p*–value (post–hoc) | .001**††† (T0 < T1; T0 < T2††) | |

| | ARCI ($n$ = 82) | KS ($n$ = 49) | $p$–value | Post–hoc |
|---|---|---|---|---|
| | | | .024* | AUD > KS† |
| | 0.65 (0.71) | 0.61 (0.64) | | |
| | 1.05 (0.70) | 0.88 (0.60) | | |
| | 1.21 (0.73) | 0.96 (0.76) | | |
| | | | *.499* | |
| | | | .066 | |
| | 1.87 (1.00) | 1.98 (1.09) | | |
| | 2.29 (1.06) | 2.37 (1.17) | | |
| | 2.41 (1.01) | 2.12 (1.01) | | |
| | | | *.271* | |
| | | | .063 | |
| | 4.85 (1.30) | 5.04 (1.27) | | |
| | 5.01 (1.22) | 5.35 (0.99) | | |
| | 5.13 (1.16) | 5.49 (0.79) | | |
| | | | *.819†††* | |
| | | | .538 | |
| | 3.96 (0.87) | 4.14 (1.00) | | |
| | 3.35 (1.04) | 3.27 (0.84) | | |
| | 3.50 (0.69) | 3.53 (0.54) | | |
| | | | *.440†††* | |
| | | | .562 | |
| | 1.11 (0.75) | 1.18 (0.81) | | |
| | 1.20 (0.78) | 1.39 (0.73) | | |
| | 1.68 (0.54) | 1.69 (0.55) | | |
| | | | *.513†††* | |
| | | | < .001*** | AUD > ARCI; AUD > KS; ARCI > KS†††† |
| | 1.51 (1.43) | 0.41 (1.02) | | |
| | 1.83 (1.57) | 0.14 (0.41) | | |
| | 2.17 (1.60) | 0.41 (0.96) | | |
| | | | *.005*†††* | |

***Table 5.2.*** Continued.

| Cognitive domain (range) | Total ($n$ = 166) | AUD ($n$ = 35) |
|---|---|---|
| Orientation (0–6) | | |
| T0 | 4.43 (1.72) | 5.63 (0.73) |
| T1 | 5.01 (1.27) | 5.69 (0.63) |
| T2 | 5.04 (1.35) | 5.66 (0.64) |
| $p$–value (post–hoc) | < .001***††† (T0 < T1; T0 < T2††) | |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; T0 = baseline/intake; T1 = after six weeks of clinical admission; T2 = at clinical discharge; † = Bonferroni; †† = Hochberg's GT2; ††† = Greenhouse–Geisser; †††† = Games–Howell; * = $p$ < .05; ** = $p$ < .005; *** = $p$ < .001.

### *Course of everyday cognitive functioning*

*Patient rating*

There was a significant main effect of time on overall everyday cognitive functioning (PCRS–TS; $F(1, 297) = 8.30$, $p = .004$, $\eta^2 = 0.027$), meaning that patients scored higher on T2 than on T1. No significant main effect of group nor a significant interaction was found. For the domain scores, significant main effects of time were found on ADL ($F(1, 297) = 9.26$, $p = .003$, $\eta^2 = 0.030$), CO ($F(1, 297) = 4.02$, $p = .046$, $\eta^2 = 0.013$) and EM ($F(1, 297) = 7.19$, $p = .008$, $\eta^2 = 0.023$), where all scores improved. A significant main effect of group was found on CO ($F(1, 297) = 9.30$, $p < .001$, $\eta^2 = 0.059$), where post–hoc tests revealed that patients with AUD scored significantly higher than those with ARCI (*M*diff = 2.09, $SD = 0.75$, $p = .017$) and those with KS (*M*diff = 3.48, $SD = 0.81$, $p < .001$). There were no significant interaction effects (see Table 5.3).

*Clinician rating*

There was a significant main effect of group on overall everyday cognitive functioning (PCRS–TS; $F(2, 345) = 102.30$, $p < .001$, $\eta^2 = 0.372$), where post–hoc tests revealed that patients with AUD scored higher than those with ARCI (*M*diff = 7.69, $SD = 2.25$) and those with KS (*M*diff = 29.59, $SD = 2.41$), and patients with ARCI scored higher than those with KS (*M*diff = 21.89, $SD = 1.80$; all $p$–values < .005). No significant main effect of time nor a significant interaction effect was found for overall everyday cognitive functioning. Significant main effects of time were found on all domain scores (ADL: $F(1, 345) = 15.68$, $p < .001$, $\eta^2 = 0.043$; CO: $F(1, 345) = 21.37$, $p < .001$, $\eta^2 = 0.058$; IP $F(1, 345) = 4.68$, $p = .031$, $\eta^2 = 0.013$; EM: $F(1, 345) = 21.81$, $p < .001$, $\eta^2 = 0.058$) and significant main effects of group

| | ARCI ($n$ = 82) | KS ($n$ = 49) | $p$–value | Post–hoc |
|---|---|---|---|---|
| | | | < .001*** | AUD > ARCI; AUD > KS; ARCI > KS†††† |
| | 4.80 (1.40) | 2.94 (1.70) | | |
| | 5.50 (0.79) | 3.69 (1.31) | | |
| | 5.56 (0.76) | 3.73 (1.58) | | |
| | | | *.052†††* | |

were found on ADL ($F$(2, 345) = 120.33, $p$ < .001, $\eta^2$ = 0.411), CO ($F$(2, 345) = 186.69, $p$ < .001, $\eta^2$ = 0.520) and IP ($F$(2, 345) = 25.92, $p$ < .001, $\eta^2$ = 0.131; see Table 5.4 for direction of the findings). There was also a significant interaction between time and group on EM ($F$(2, 345) = 3.49, $p$ = .032, $\eta^2$ = 0.019), showing that emotional lability of patients with AUD did not change over time, while both patients with ARCI and those with KS scored lower on T2 than on T1.

***Correlation between changes in cognitive performance and everyday cognitive functioning***

Changes in overall cognitive performance (MoCA–TS) were positively correlated to changes in overall everyday cognitive functioning (PCRS–TS), as rated by both the patient ($r$(287) = 0.134, $p$ = .012) and the clinician ($r$(297) = 0.256, $p$ < .001).

On an exploratory basis, correlations between all change–scores of the MoCA and the PCRS were calculated for the total sample and for all three groups separately (See Table 5.5 and 5.6). Main findings were that overall, correlations were higher for the clinician rating than for the patient rating, and higher for patients with KS followed by those with ARCI and AUD respectively. For the latter, correlations mostly centred zero. The highest correlations were found in patients with KS, where both the change scores of the MoCA–TS and the MoCA–DS orientation correlated significantly with all PCRS–scores of the clinician.

***Table 5.3.*** Means and standard deviations (*SD*) of the Patient Competency Rating Scale domain scores (PCRS–DS) and total score (PCRS–TS) on two assessment points rated by **the patient** for the total sample and split per group. Post–hoc gives a description of the direction of significant differences between groups (column), between assessments (row) and the interaction between groups and assessments (in italics).

| Cognitive domain (range) | Total | AUD |
|---|---|---|
| | (*n* = 300) | (*n* = 53) |
| Activities of daily living (8–40) | | |
| T1 | 34.11 (5.50) | 35.38 (5.43) |
| T2 | 35.05 (4.45) | 36.15 (3.82) |
| *p*–value | .003** | |
| Cognitive abilities (8–40) | | |
| T1 | 31.73 (5.61) | 34.23 (4.55) |
| T2 | 32.53 (5.13) | 34.34 (4.46) |
| *p*–value | .046* | |
| Interpersonal abilities (7–35) | | |
| T1 | 27.58 (4.88) | 28.45 (4.51) |
| T2 | 27.90 (4.62) | 29.19 (4.22) |
| *p*–value | .128 | |
| Emotional lability (7–35) | | |
| T1 | 24.52 (4.92) | 23.89 (4.67) |
| T2 | 25.19 (4.80) | 24.92 (4.83) |
| *p*–value | .008* | |
| Total score (30–150) | | |
| T1 | 117.94 (18.16) | 121.94 (16.50) |
| T2 | 120.66 (16.51) | 124.60 (15.20) |
| *p*–value | .004** | |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; T1 = after six weeks of clinical admission; T2 = at clinical discharge; † = Hochberg's GT2; * = $p < .05$; ** = $p < .005$; *** = $p < .001$.

| | ARCI (*n* = 153) | KS (*n* = 94) | *p*–value | Post–hoc† |
|---|---|---|---|---|
| | | | .098 | |
| | 33.54 (6.01) | 34.34 (4.50) | | |
| | 34.90 (4.66) | 34.67 (4.38) | | |
| | | | *.174* | |
| | | | < .001*** | AUD > ARCI; AUD > KS |
| | 31.54 (5.67) | 30.62 (5.67) | | |
| | 32.84 (5.01) | 30.99 (5.31) | | |
| | | | *.162* | |
| | | | .131 | |
| | 27.24 (5.10) | 27.66 (4.68) | | |
| | 27.63 (4.86) | 27.61 (4.35) | | |
| | | | *.435* | |
| | | | .679 | |
| | 24.43 (4.96) | 25.02 (4.99) | | |
| | 25.31 (4.99) | 25.13 (4.52) | | |
| | | | *.252* | |
| | | | .130 | |
| | 116.75 (19.09) | 117.64 (17.34) | | |
| | 120.69 (16.83) | 118.39 (16.42) | | |
| | | | *.197* | |

***Table 5.4.*** Means and standard deviations (*SD*) of the Patient Competency Rating Scale domain scores (PCRS–DS) and total score (PCRS–TS) on two assessment points rated by **the clinician** for the total sample and split per group. Post–hoc gives a description of the direction of significant differences between groups (column), between assessments (row) and the interaction between groups and assessments (in italics).

| Cognitive domain (range) | Total | AUD | ARCI | KS |
|---|---|---|---|---|
| | (*n* = 348) | (*n* = 58) | (*n* = 179) | (*n* = 111) |
| Activities of daily living (8–40) | | | | |
| T1 | 25.83 (7.22) | 30.98 (5.56) | 28.02 (6.24) | 19.59 (4.94) |
| T2 | 26.93 (7.37) | 32.34 (5.38) | 29.01 (6.00) | 20.76 (6.07) |
| *p*–value | < .001*** | | | |
| Cognitive abilities (8–40) | | | | |
| T1 | 24.67 (7.62) | 29.93 (5.75) | 27.53 (6.04) | 17.31 (4.93) |
| T2 | 26.02 (7.64) | 32.05 (4.59) | 28.57 (5.78) | 18.77 (6.04) |
| *p*–value | < .001*** | | | |
| Interpersonal abilities (7–35) | | | | |
| T1 | 23.90 (4.63) | 25.43 (4.33) | 24.71 (4.32) | 21.80 (4.59) |
| T2 | 23.13 (5.24) | 25.29 (5.25) | 23.83 (4.91) | 20.88 (4.99) |
| *p*–value | .031* | | | |
| Emotional lability (7–35) | | | | |
| T1 | 23.44 (4.37) | 23.29 (4.20) | 23.62 (4.28) | 23.23 (4.65) |
| T2 | 21.77 (4.77) | 23.16 (4.80) | 21.82 (4.70) | 20.97 (4.74) |
| *p*–value | < .001*** | | | |
| Total score (30–150) | | | | |
| T1 | 97.84 (19.67) | 109.61 (16.66) | 103.88 (16.87) | 81.93 (15.09) |
| T2 | 97.86 (21.18) | 112.84 (17.17) | 103.22 (17.82) | 81.38 (17.56) |
| *p*–value | .493 | | | |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; T1 = after six weeks of clinical admission; T2 = at clinical discharge; † = Hochberg's GT2; * = $p < .05$; ** = $p < .005$; *** = $p < .001$.

| | *p*–value | Post–hoc† |
|---|---|---|
| | < .001*** | AUD > ARCI; AUD > KS; ARCI > KS |
| | *.870* | |
| | < .001*** | AUD > ARCI; AUD > KS; ARCI > KS |
| | *.435* | |
| | < .001*** | AUD > KS; ARCI > KS |
| | *.576* | |
| | .162 | |
| | *.032** | AUD: T1 = T2; ARCI: T1 > T2; KS: T1 > T2; T1: AUD = ARCI = KS; T2: AUD > KS |
| | < .001*** | AUD > ARCI; AUD > KS;ARCI > KS |
| | *.266* | |

***Table 5.5.*** Correlations between the change scores of the Montreal Cognitive Assessment Domain Scores (MoCA–DS), Total Score (MoCA–TS) and Memory Index Score (MoCA–MIS), and the change scores of the Patient Competency Rating Scale Domain Scores (PCRS–DS) and Total Score (PCRS–TS) between the sixth week of admission (T1) and at clinical discharge (T2) for **the patient** for the total sample and split per group.

| | | | Total (*n* = 287) | | |
|---|---|---|---|---|---|
| MoCA | | | PCRS | | |
| | ADL | CO | IP | EM | TS |
| EF | −0.02 (.395) | −0.01 (.448) | −0.03 (.294) | 0.01 (.418) | −0.01 (.413) |
| VA | 0.15 (.006)* | 0.05 (.190) | 0.03 (.314) | 0.01 (.436) | 0.08 (.100) |
| ACW | 0.05 (.179) | 0.12 (.019)* | 0.07 (.124) | 0.09 (.069) | 0.11 (.038)* |
| L | 0.08 (.088) | 0.08 (.101) | 0.12 (.018)* | 0.03 (.320) | 0.09 (.056) |
| AR | −0.03 (.326) | 0.09 (.062) | −0.02 (.390) | −0.01 (.443) | 0.02 (.388) |
| M | 0.06 (.172) | 0.00 (.499) | −0.02 (.382) | −0.03 (.334) | 0.01 (.464) |
| O | 0.12 (.024)* | 0.12 (.021)* | 0.09 (.073) | 0.07 (.124) | 0.12 (.019)* |
| TS | 0.15 (.006)* | 0.14 (.009)* | 0.08 (.089) | 0.05 (.184) | 0.13 (.012)* |
| MIS | 0.04 (.272) | 0.06 (.172) | 0.01 (.437) | 0.02 (.400) | 0.04 (.260) |
| | | | ARCI (*n* = 149) | | |
| MoCA | | | PCRS | | |
| | ADL | CO | IP | EM | TS |
| EF | −0.02 (.408) | −0.06 (.234) | −0.06 (.232) | −0.00 (.848) | −0.04 (.296) |
| VA | 0.19 (.011)* | 0.11 (.087) | 0.05 (.294) | 0.00 (.496) | 0.11 (.098) |
| ACW | −0.02 (.425) | 0.11 (.101) | 0.07 (.209) | 0.10 (.104) | 0.08 (.167) |
| L | 0.04 (.304) | 0.09 (.131) | 0.10 (.107) | 0.04 (.307) | 0.09 (.151) |
| AR | 0.06 (.239) | 0.19 (.011)* | 0.05 (.272) | 0.10 (.124) | 0.12 (.068) |
| M | 0.09 (.138) | 0.03 (.376) | 0.03 (.339) | 0.04 (.332) | 0.06 (.251) |
| O | 0.11 (.092) | 0.14 (.047)* | 0.06 (.240) | 0.11 (.095) | 0.13 (.062) |
| TS | 0.17 (.019)* | 0.20 (.007)* | 0.11 (.087) | 0.13 (.061) | 0.19 (.011)* |
| MIS | 0.02 (.400) | 0.02 (.403) | 0.03 (.341) | 0.03 (.379) | 0.03 (.359) |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; ADL = Activities of Daily Living; CO = Cognitive abilities; IP = Interpersonal abilities; EM = Emotional lability; TS = Total Score; EF = Executive functioning; VA = Visuospatial abilities; ACW = Attention, concentration and working memory; L = Language; AR = Abstract reasoning; M = Memory; O = Orientation; * = p < .05; ** = p < .005; *** = p < .001.

| | | AUD ($n$ = 51) | | |
|---|---|---|---|---|
| | | PCRS | | |
| ADL | CO | IP | EM | TS |
| −0.04 (.399) | −0.15 (.155) | −0.15 (.152) | −0.31 (.013)* | −0.22 (.065) |
| 0.13 (.190) | −0.06 (.330) | −0.16 (.131) | −0.17 (.110) | −0.08 (.282) |
| 0.06 (.328) | 0.02 (.450) | −0.02 (.445) | −0.03 (.426) | 0.02 (.455) |
| 0.19 (.088) | −0.11 (.230) | 0.02 (.454) | −0.22 (.061) | −0.04 (.401) |
| −0.13 (.182) | −0.12 (.210) | −0.14 (.170) | −0.13 (.187) | −0.18 (.109) |
| 0.09 (.259) | −0.13 (.184) | −0.19 (.090) | −0.31 (.013)* | −0.17 (.111) |
| 0.07 (.323) | −0.24 (.045)* | −0.31 (.013)* | −0.11 (.217) | −0.20 (.079) |
| 0.12 (.198) | −0.19 (.087) | −0.25 (.039)* | −0.36 (.005)* | −0.22 (.060) |
| 0.10 (.241) | −0.16 (.129) | −0.23 (.052) | −0.35 (.006)* | −0.21 (.073) |
| | | KS ($n$ = 87) | | |
| | | PCRS | | |
| ADL | CO | IP | EM | TS |
| 0.00 (.496) | 0.14 (.107) | 0.07 (.251) | 0.18 (.047)* | 0.12 (.130) |
| 0.09 (.211) | −0.01 (.482) | 0.05 (.315) | 0.07 (.251) | 0.06 (.283) |
| 0.17 (.062) | 0.20 (.034)* | 0.11 (.154) | 0.11 (.159) | 0.19 (.042)* |
| 0.11 (.158) | 0.13 (.119) | 0.24 (.012)* | 0.12 (.132) | 0.18 (.047)* |
| −0.17 (.062) | −0.05 (.317) | −0.10 (.171) | −0.16 (.067) | −0.15 (.085) |
| −0.08 (.229) | −0.02 (.414) | −0.05 (.325) | −0.00 (.490) | −0.05 (.327) |
| 0.17 (.063) | 0.21 (.026)* | 0.25 (.009)* | 0.09 (.204) | 0.22 (.019)* |
| 0.14 (.101) | 0.22 (.022)* | 0.23 (.018)* | 0.15 (.080) | 0.23 (.017)* |
| 0.03 (.405) | 0.19 (.043)* | 0.05 (.318) | 0.12 (.135) | 0.12 (.125) |

***Table 5.6.*** Correlations between the change scores of the Montreal Cognitive Assessment Domain Scores (MoCA–DS), Total Score (MoCA–TS) and Memory Index Score (MoCA–MIS), and the change scores of the Patient Competency Rating Scale Domain Scores (PCRS–DS) and Total Score (PCRS–TS) between the sixth week of admission (T1) and at clinical discharge (T2) for **the clinician** rating for the total sample and split per group.

| | | | Total (*n* = 297) | | |
|---|---|---|---|---|---|
| MoCA | | | PCRS | | |
| | ADL | CO | IP | EM | TS |
| EF | 0.06 (.151) | 0.12 (.023)* | 0.05 (.186) | 0.09 (.060) | 0.10 (.040)* |
| VA | 0.12 (.022)* | 0.20 (< .001)*** | 0.07 (.116) | 0.13 (.011)* | 0.17 (.002)** |
| ACW | 0.12 (.020)* | 0.12 (.017)* | 0.07 (.105) | 0.01 (.407) | 0.10 (.036)* |
| L | 0.08 (.082) | 0.13 (.015)* | 0.03 (.277) | −0.01 (.445) | 0.08 (.097) |
| AR | 0.02 (.359) | 0.14 (.008)* | 0.16 (.003)** | 0.08 (.085) | 0.13 (.013)* |
| M | 0.08 (.084) | 0.04 (.265) | −0.02 (.385) | −0.02 (.352) | 0.02 (.338) |
| O | 0.21 (< .001)*** | 0.21 (< .001)*** | 0.16 (.003)** | 0.15 (.005)* | 0.23 (< .001)*** |
| TS | 0.23 (< .001)*** | 0.30 (< .001)*** | 0.16 (.004)** | 0.13 (.015)* | 0.26 (< .001)*** |
| MIS | 0.08 (.085) | 0.02 (.377) | −0.01 (.465) | −0.03 (.323) | 0.02 (.365) |
| | | | ARCI (*n* = 154) | | |
| MoCA | | | PCRS | | |
| | ADL | CO | IP | EM | TS |
| EF | 0.08 (.174) | 0.16 (.026)* | 0.07 (.206) | 0.04 (.311) | 0.11 (.091) |
| VA | 0.15 (.033)* | 0.19 (.009)* | 0.13 (.049)* | 0.20 (.006)* | 0.21 (.005)** |
| ACW | 0.11 (.096) | 0.18 (.014)* | 0.05 (.254) | −0.04 (.293) | 0.10 (.118) |
| L | 0.11 (.086) | 0.21 (.004)** | 0.20 (.007)* | 0.03 (.361) | 0.17 (.016)* |
| AR | 0.02 (.392) | 0.10 (.099) | 0.14 (.040)* | 0.04 (.302) | 0.10 (.116) |
| M | 0.04 (.299) | 0.03 (.356) | −0.04 (.307) | −0.05 (.251) | −0.01 (.477) |
| O | 0.16 (.028)* | 0.18 (.013)* | 0.11 (.081) | −0.01 (.451) | 0.14 (.044)* |
| TS | 0.22 (.003)** | 0.33 (< .001)*** | 0.20 (.008)* | 0.06 (.242) | 0.25 (< .001)*** |
| MIS | −0.00 (.496) | −0.05 (.263) | −0.08 (.171) | −0.06 (.224) | −0.06 (.235) |

Note: AUD = Alcohol Use Disorder; ARCI = Alcohol–Related Cognitive Impairments; KS = Korsakoff's Syndrome; ADL = Activities of Daily Living; CO = Cognitive abilities; IP = Interpersonal abilities; EM = Emotional lability; TS = Total Score; EF = Executive functioning; VA = Visuospatial abilities; ACW = Attention, concentration and working memory; L = Language; AR = Abstract reasoning; M = Memory; O = Orientation; * = p < .05; ** = p < .005; *** = p < .001.

| | | AUD ($n$ = 52) | | |
|---|---|---|---|---|
| | | PCRS | | |
| ADL | CO | IP | EM | TS |
| −0.04 (.398) | −0.03 (.423) | 0.01 (.479) | 0.14 (.164) | 0.03 (.418) |
| 0.10 (.244) | 0.22 (.057) | 0.03 (.415) | 0.27 (.029)* | 0.20 (.074) |
| 0.18 (.099) | −0.06 (.346) | 0.10 (.233) | 0.13 (.182) | 0.11 (.210) |
| 0.13 (.183) | 0.08 (.300) | −0.22 (.056) | −0.13 (.173) | −0.05 (.354) |
| −0.11 (.223) | −0.03 (.417) | 0.01 (.470) | 0.02 (.441) | −0.03 (.410) |
| 0.32 (.011)* | 0.11 (.225) | 0.00 (.497) | 0.16 (.129) | 0.19 (.091) |
| 0.17 (.110) | 0.10 (.244) | −0.00 (.498) | 0.20 (.279) | 0.15 (.139) |
| 0.25 (.039)* | 0.12 (.192) | −0.02 (.456) | 0.21 (.069) | 0.18 (.097) |
| 0.21 (.064) | 0.07 (.309) | −0.01 (.474) | 0.18 (.101) | 0.15 (.148) |
| | | KS ($n$ = 91) | | |
| | | PCRS | | |
| ADL | CO | IP | EM | TS |
| 0.09 (.204) | 0.12 (.123) | 0.06 (.304) | 0.14 (.092) | 0.14 (.101) |
| 0.07 (.272) | 0.21 (.022)* | −0.04 (.370) | −0.07 (.272) | 0.06 (.283) |
| 0.12 (.129) | 0.10 (.178) | 0.09 (.200) | 0.05 (.321) | 0.12 (.136) |
| 0.03 (.408) | 0.02 (.419) | −0.08 (.226) | 0.03 (.388) | −0.00 (.500) |
| 0.09 (.198) | 0.31 (.001)** | 0.30 (.002)** | 0.22 (.018)* | 0.31 (.002)** |
| 0.02 (.421) | 0.03 (.391) | 0.07 (.266) | −0.04 (.338) | 0.02 (.44) |
| 0.30 (.002)** | 0.30 (.002)** | 0.28 (.004)** | 0.32 (.001)** | 0.39 (< .001)*** |
| 0.25 (.008)* | 0.36 (< .001)*** | 0.21 (.022)* | 0.21 (.022)* | 0.34 (< .001)*** |
| 0.18 (.047)* | 0.14 (.097) | 0.13 (.108) | −0.05 (.330) | 0.13 (.113) |

# Discussion

Aims of this study were to explore the course of cognitive performance and subjective everyday cognitive functioning during treatment towards abstinence and recovery in patients with AUD, ARCI and KS in a large clinical sample, and to determine if changes in cognitive performance are related to changes in everyday cognitive functioning. It was found that cognitive performance improved significantly over the course of treatment and differed between groups. Everyday cognitive functioning also improved significantly over time, according to both the patient and the clinician. Significant differences between groups were only found on the clinician rating. For both cognitive performance and everyday cognitive functioning, patients with AUD scored higher than those with ARCI and KS, and patients with ARCI scored higher than those with KS. Finally, changes in overall cognitive performance were positively correlated to changes in overall everyday cognitive functioning.

Overall cognitive performance improved significantly between intake and the sixth week of clinical admission, supporting our hypothesis. In these first six weeks, detoxification and recovery are the main goals of treatment. Although neither being abstinent nor abstinence duration were previously found to be related to cognitive performance (Bruijnen, Jansen, et al., 2019), our findings are in line with the recommendation to perform extended neuropsychological assessment after a minimum of six weeks of abstinence, as this seems to be a sufficient period of time for cognitive functioning to recover to a baseline (Walvoort et al., 2013). Particularly in patients with KS, it is argued that cognitive impairments are mostly irreversible and thus may not recover above a ceiling level after abstinence is reached (Arts et al., 2017). When comparing cognitive performance at discharge in our study to findings by Oudman et al. (2014), we find very similar results. In their study that included 30 patients with KS who were in the chronic phase of the syndrome and had been abstinent for a minimum of six months, a mean MoCA–TS of 18.1 (*SD* = 3.9) was found, which is very comparable to our finding of 18.7 (*SD* = 3.8). We found the improvement of cognitive performance in all three groups between the sixth week of admission and clinical discharge, not supporting our hypothesis that patients with AUD or KS would not improve further during treatment. This means that all patients with AUD can benefit from prolonged clinical treatment. As the time between T1 and T2 varied between patients, additional analyses were performed to examine a possible relation between admission time and cognitive performance, which was not found. Exploration of the domain scores showed that patients with KS did not change on the memory domain, while patients with ARCI improved over all three assessments. Taking the length of clinical stay and the number of readmissions into account, patients with ARCI recover most from short–term clinical treatment. However, these alcohol–related cognitive impairments may increase the risk of readmission (resulting from a relapse into alcohol use), making this the most vulnerable group of patients.

Another finding is that patients rate their own everyday cognitive functioning to be better than that rated by clinicians. While clinician ratings are significantly lower in patients with KS, followed by patients with ARCI and those with AUD respectively, and thus supporting our hypothesis, patient ratings did not differ between groups. This finding is in line with the literature in which patients do not always report subjective complaints because of a lack of insight into their own cognitive deficits (Walvoort et al., 2016). As opposed to the patient ratings, clinicians do not report a significant change in overall everyday cognitive functioning over the course of treatment, which does not support our hypothesis. This finding can be explained when looking at the four domains separately. As scores for activities of daily living and cognitive abilities improved significantly, scores for interpersonal abilities and emotional lability significantly declined over time. Patients with AUD and ARCI reported significant improvements in overall everyday cognitive functioning, thus partly supporting our hypothesis, and also on the domains activities of daily living, cognitive abilities and emotional lability. These changes may be influenced by the fact that patients were probably in a better emotional state when completing the second assessment, as they were (soon to be) clinically discharged.

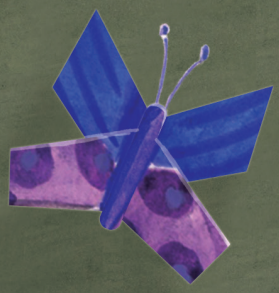
Although several significant positive correlations were found between changes in cognitive performance and changes in everyday cognitive functioning, the effect sizes remained mostly small to medium. This supports the literature that cognitive performance on objective measures is not predictive for cognitive deficits in the absence of subjective experiences of these deficits (Horner et al., 1999). Correlations were highest between overall cognitive performance and the clinician ratings of everyday cognitive functioning. Interestingly, changes in cognitive performance on orientation also correlated significantly with everyday cognitive functioning and correlations were overall higher for patients with KS. These findings on correlations between cognitive performance and everyday cognitive functioning partly support our hypothesis.

There are several strengths to this study. First, being able to include a large group of patients and follow them over a significant amount of time in an inpatient setting, makes the findings highly clinically relevant and generalisable to the population. Second, due to an extensive (multidisciplinary) diagnostic process, it was possible to compare three well–described patient groups. Third, because the patients were clinically admitted information from multiple sources, including from clinicians who were familiar with the patient and his/her abilities, could be included. Finally, two instruments (MoCA and PCRS) were used that are freely available and are easy to administer.

A limitation to the study is that not all patients who were admitted to the clinic during data collection could be included. Despite the fact that almost one–third of patients were excluded from the study, we strongly argue that this group does not represent a subsample of patients. As is explained in detail in the Participants section, exclusion was mostly based on the lack of implementation of the MoCA in the first few years of the study, readmission of patients during the study or early discharge against medical advice. The results also showed that the included patients were still representative for the total sample.

In summary, this study describes the course of cognitive performance on the MoCA during treatment towards abstinence and recovery, in three patient groups. The study confirms that patients with AUD had the highest MoCA scores, followed by patients with ARCI and those with KS respectively. Surprisingly, all three groups improved significantly over time. It can be concluded that performance on the memory domain is the best predictor for KS: scores were significantly lowest and no improvement occurred in the first six weeks of abstinence and recovery, where patients with AUD and those with ARCI scored higher and improved over the course of treatment. As for everyday cognitive functioning, it was confirmed that patients have a lack of insight into their cognitive deficits, as scores of all three patient groups were comparable while the clinician reports were significantly different between groups. Interestingly, by comparing changes in cognitive performance to changes in everyday cognitive functioning, it was found that especially for patients with KS, changes in overall cognitive performance and on the domain orientation relate positively to changes in everyday cognitive functioning.

Buiten het werk heb ik zoveel steun gehad in alle vrienden en bekenden om mij heen. Allereerst de lieve meiden van ‘ut Vlasrooth’: Mieke, Laura, Marie–José, Lieke, Lieke, Silvie, Kirsten, Monique, Kim en Chantalle. We go way back! Op de basisschool hebben we elkaar leren kennen en door de jaren heen zijn we elkaar nooit echt uit het oog verloren. Jullie waren er als ik afleiding nodig had, gezelligheid zocht en gewoon onnozel mee wilde lachen. Jullie waren er ook als ik steun nodig had gedurende het traject dat Koos en ik de afgelopen jaren (naast alles!) hebben doorlopen. Jullie waren er toen ik het blijde nieuws kon delen. De groep is groot geworden, eerst met alle vriendjes (inmiddels veelal mannen) en vervolgens de kleine ‘Vlaskoters’ zoals ik ze graag wil noemen. Ik geniet ervan als we samen zijn en alle kinderen samen kunnen spelen. Waarom is het toch, dat we enkel onze gevoelens uiten tijdens de late uurtjes van een (dronken) Ossefeest of kermisavond? Ik hou van jullie en dat mag gezegd worden!



# Chapter 6

## Cognitive impairments in patients with Gamma–Hydroxybutyrate (GHB) use disorder predict relapse

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## Abstract

The recreational use of Gamma–hydroxybutyrate (GHB) is associated with frequent overdoses, coma and the risk of developing GHB use disorder (GUD). Several studies suggest negative effects of GHB use or related comas on cognition. Since relapse rates are particularly high in GUD, and cognitive impairment has been associated with relapse in other substance use disorders, we aim to investigate the relationship between GHB use, self–reported comas and cognitive impairment, and the role of cognitive impairment in relapse into GHB use after detoxification in GUD patients. In this prospective cohort study a consecutive series of patients with GUD ($n$ = 137) admitted for detoxification were recruited at six addiction care facilities in the Netherlands. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairments before and after detoxification. Follow–up for the assessment of relapse in GHB use was after three months. A substantial number of patients with GUD screened positive for cognitive impairment before (56.3%) and after (30.6%) detoxification. Most patients showed impairment on the MoCA domain memory (58.8%). Cognitive impairment was not related to the severity of GUD or number of GHB–induced comas. Proportionately more patients who relapsed performed under the cut–off of the MoCA before detoxification than those who remained abstinent. Regression analysis showed that only performance on the MoCA domain memory predicted relapse. Cognitive impairment seems highly prevalent among patients with GUD, possibly related to the risk of relapse. The absence of a relationship between the severity of GUD, level of GHB use, the number of GHB–induced comas and cognitive impairment suggest that other factors may also contribute to the observed cognitive impairment. Current findings warrant clinical attention for cognitive impairment in patients with GUD, for instance by screening for cognitive impairment using the MoCA, and a full neuropsychological assessment after detoxification.

# Introduction

Gamma–hydroxybutyrate (GHB) is a GHB and $GABA_B$ receptor agonist and an increasingly popular party drug, mainly due to its euphoric, sociability and sexually stimulating effects (Sumnall et al., 2008; Brennan & van Hout, 2014; Whelan et al., 2014; Bosch et al., 2015; Bosch et al., 2017; European Monitoring Centre for Drugs and Drug Addiction, 2017). However, GHB use is also associated with frequent overdoses, comas (Kamal et al., 2017; Beurmanjer et al., 2019), hospital admissions (Dijkstra et al., 2017; Grund et al., 2018), and a risk of physical dependence (Nicholson & Balster, 2001; van Noorden et al., 2016; Dijkstra et al., 2017). In line with DSM–5 criteria for SUD (APA, 2013) physical GHB dependence is commonly part of GHB use disorder (GUD), with a pattern of continued use despite negative consequences, craving for GHB and loss of control over GHB intake (Kamal et al., 2017).

Patients with GUD generally show high drop–out and relapse rates, up to 50% – 60% relapse within three months after detoxification (Dijkstra et al., 2017; van Noorden et al., 2017; Beurmanjer et al., 2019). The readmission rate of patients with GUD is twice as high as seen in patients with alcohol or cannabis use disorder (van Noorden et al., 2017). It is unknown why relapse rates are higher among patients with GUD compared to other SUD. It has been suggested that the prosocial effects of GHB with few noticeable downsides could play a part in the high relapse rates (Bosch et al., 2015; Beurmanjer et al., 2019). Other suggested explanations are the high levels of anxiety in patients with GUD (Beurmanjer et al., 2019), similar to for example patients with alcohol use disorder (Schellekens et al., 2015).

Another aspect that might be particularly relevant in the context of relapse in patients with GUD is cognitive impairment. In general, cognitive impairment has been associated with relapse in several SUD, e.g. alcohol (Czapla et al., 2015), cocaine (Verdejo–García et al., 2014) and opioids (Ma et al., 2019). While research on cognitive impairment in GUD is limited, several studies suggest negative effects of GHB on cognition. For instance, a double blind, placebo controlled study with healthy volunteers showed that GHB intoxication temporarily impaired working– and episodic memory, in a dose dependent manner (Carter et al., 2009). Recent studies also suggest that GHB–induced comas are associated with (verbal) memory impairments in patients with GUD. In this cross–sectional study GHB–induced comas were also associated with alterations in long–term memory networks and lower hippocampus/lingual gyrus activity while performing memory tasks (Raposo Pereira et al., 2018a; Raposo Pereira et al., 2018b).

GHB–induced comas are very common in GUD patients, with 84% of users having experienced GHB–induced comas at least once, and often even on a daily basis (Beurmanjer et al., 2019). Therefore, cognitive impairment might result from excessive GHB use and can potentially be an important factor in the high relapse rates observed in GUD patients. To our knowledge no studies on the relationship between cognitive impairment and relapse in patients with GUD have been published to date. This prospective cohort study aimed to investigate in patients with GUD: 1) the association between cognitive impairment, the number of GHB–induced comas and severity of GHB use; and 2) the association between cognitive impairment and relapse in GHB use after detoxification.

# Methods

### Design

This study is a prospective, observational, multicentre cohort study, part of a larger monitor of patients with GUD. Due to the observational design, the study was exempted from medical ethical review by the Medical Ethical Committee of the Medical Spectrum Twente. Part of the data of the monitor has already been published as an open label trial with baclofen (Beurmanjer et al., 2018).

### Participants

A consecutive series of patients with GUD (according to DSM–IV criteria of substance dependence, APA, 1994) who were admitted for detoxification at one of six participating addiction health care centres in the Netherlands (i.e. IrisZorg, Mondriaan, Novadic–Kentron, Tactus Verslavingszorg, Victas and Verslavingszorg Noord–Nederland) were recruited ($n$ = 137). Inclusion criteria were an age of 18–65 years, a need for inpatient GHB detoxification, and comprehension of the Dutch language. One exclusion criterion was the presence of acute psychiatric problems interfering with study participation, such as mania or acute psychosis. A physician screened patients on these criteria before detoxification. All patients signed informed consent, before they were included in the study.

### Materials

*Demographic data*

Demographic data such as sex, date of birth, ethnicity, housing situation, source of income and level of education were collected through self–report.

*Measurements of the Addictions for Triage and Evaluation*

The MATE 2.1 (Schippers et al., 2011) is a structured clinical interview that measures the history, frequency and consequences of drug use, including medical, social and psychological problems, and part of it is based on the Composite International Diagnostic Interview (CIDI; WHO, 1997). For this study section 1 'Substance Use' was used to assess GHB and other substance use patterns. During this structured interview patients were asked about their substance use over the past 30 days (number of days and amount used) and lifetime (total years of use of at least three days per week). The MATE 2.1 has a good inter–rater reliability, ranging between 0.75 and 0.92 (Schippers et al., 2010).

*GHB questionnaire*

In addition to the questions on GHB use in the MATE 2.1, the GHB questionnaire was included to obtain more detailed information on GHB use patterns (Dijkstra et al., 2017). The original questionnaire has 28 questions regarding motivation for GHB use, first introduction

to GHB, location of use, frequency of use, dose, duration of use, number of comas, number of hospital admissions and experienced withdrawal symptoms. For this study we included five questions to assess the frequency of GHB use, the dose of GHB used (in millilitres), the duration of GHB use (in months), the duration of daily GHB use (in months) and how often participants experienced a coma due to GHB use in their lifetime.

*Montreal Cognitive Assessment*

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to screen for substance–induced cognitive impairment (Bruijnen, Jansen, et al., 2019). It consists of 12 items measuring: executive and visuospatial functioning; attention, concentration and working memory (referred to as 'attention' from now on); language; abstract reasoning; memory; and orientation. For this study the Dutch MoCA version 7.1 and alternate form 7.2 were used at T1 and T2, respectively. Administration of the MoCA takes approximately 15 minutes. The MoCA Total Score (MoCA–TS) is calculated by summing scores on all items with a maximum score of 30 points. A higher score represents better cognitive performance. An adjustment for level of education is applied in which participants with a low level of education receive two extra points, and participants with an average level of education receive one extra point to their total score, while maintaining a maximum score of 30 points (see Bruijnen, Jansen, et al., (2019) for a description of how level of education was measured). Originally, a cut–off score of 25 or lower was used as an indicator of cognitive impairment (Nasreddine et al., 2005). The MoCA is widely used in clinical practice for screening for cognitive impairment in various populations and has a moderate to excellent inter–rater reliability between $\kappa = 0.46$ and $\kappa = 0.94$ (Cumming et al., 2020).

*Treatment outcome*

Three months after detoxification all patients were contacted either in person (when the patient was still in treatment) or by phone (when patients where no longer in treatment). During this interview patients were asked whether they had relapsed in GHB use in the past three months. Patients were considered non–relapse if they had used GHB less than five times in the past three months. This self–reported abstinence was not confirmed using systematic urine or blood tests, due to the narrow timeframe in which GHB can be detected as a result of its short half–life (Abanades et al., 2007). When patients could not be reached, a predetermined close contact of the patient was approached about treatment outcome. In cases where nobody was available, patient records were examined for treatment outcome or (former) counsellors were approached. The last clinical observation was carried forward in this case.

***Procedure***

Patients were informed about the study before admission to the clinic (before detoxification). After informed consent was signed, demographic data were collected and the MATE 2.1 and MoCA 7.1 were administered by a trained nurse or psychologist prior to detoxification (T1). After detoxification, on average 20.1 days later, MoCA 7.2 was administered (T2). Another three months after detoxification patients were contacted to assess relapse into GHB use (T3). Data were collected between January 2014 and May 2015.

***Analyses***

The patient characteristics for age, sex, substance use, MoCA Domain Scores (MoCA–DS), Total Score (MoCA–TS) and the number of patients scoring below the cut–off score were summarized using descriptive statistics for both T1 and T2. Differences between MoCA–DS and –TS on T1 and those on T2 were analysed using repeated measures ANOVAs, and a chi–square test was used for the cut–off scores. Only patients with data available for both time–points were included in these analyses.

For each patient a total GHB exposure score was calculated by taking 'the average daily dose of GHB' times 'the number of days GHB was used in the past thirty days' times 'the months of daily GHB use'. To study the relationship between MoCA–TS, the number of comas and GHB use (dose per day, months of use, months of daily use, and the GHB exposure score) Pearson or Spearman correlations were used as appropriate.

The difference in MoCA–DS and –TS between relapse and non–relapse patients at T3 was analysed using MANOVA. In order to assess the predictive value of the MoCA, a backward logistic regression was performed with relapse as the dependent variable and MoCA scores (all –DS and –TS) as the independent variables. Two–sided *p*–values of $< .05$ were considered statistically significant. Data were analysed with IBM SPSS version 26.0.

# Results

### *Patient characteristics*

Data of 103 patients were analysed in this study, this included 80 MoCA measurements at T1 and 62 at T2. In total 39 patients had completed the MoCA at both T1 and T2. These 39 patients did not differ from patients with a MoCA on either T1 or T2 regarding sex, age, GHB dose, length of daily GHB use, number of comas and MoCA performance. The mean age was 28.5 years (*SD* = 6.47) and 68% were men. The mean duration of daily GHB use was 31.3 months (*SD* = 32.61), with a mean of 89.9 ml GHB per day (*SD* = 52.60). GHB–induced comas were common, with 41.4% reporting 5 or less GHB comas, 18.4% between 6 and 19 times, 19.5% between 20 and 50 times, and 20.7% reported to have experienced more than 50 comas in their lifetime. The highest reported co–morbid substance of use in the past 30 days was nicotine (83,7%), followed by stimulants (50%), alcohol (43,5%), cannabis (33,7%) and cocaine (33,7%), respectively.

### *Performance on the Montreal Cognitive Assessment*

On average, patients scored a MoCA–TS of 24.2 points (*SD* = 3.01) at T1 and 25.8 points (*SD* = 2.78) at T2, with a trend towards significance (Wilks' $\lambda$ = .90, $F(1, 38) = 4.08$, $p = .051$) for patients with a MoCA on both T1 and T2 (Table 6.1). Fewer patients scored below the cut–off score on T2 than on T1, indicating an improvement ($\chi^2(1) = 5.21$ $p = .022$). In total 27 patients improved their scores between T1 and T2, 5 had the same score and 7 had a lower score. On domain level, patients performed lowest on Memory and highest on Orientation on both T1 and T2. No significant differences were observed on domain level between T1 and T2.

### *Correlation between cognitive performance, and GHB use characteristics*

MoCA–TS on both T1 and T2 did not correlate significantly with any of the investigated GHB use characteristics (i.e. the number of comas, GHB dose, total length of GHB use, length of daily GHB use and the GHB exposure score; Table 6.2). There was only a significant correlation between sex and scoring above or below the MoCA cut–off (Table 6.3).

### *Relation between cognitive performance and relapse*

Non–relapse patients at T3 scored higher on the MoCA–DS attention, memory and MoCA–TS at T1 in comparison to patients who had relapsed at T3. Also, more of the non–relapse patients scored above the MoCA–TS cut off–score at T1, compared to patients who relapsed at T3. No relationship was found between treatment outcome (relapse or non–relapse) and cognitive performance (MoCA–DS or –TS) on T2 (Table 6.4).

***Table 6.1.*** Means, standard deviations (*SD*) and proportion correct per domain on the Montreal Cognitive Assessment (MoCA) Domain Scores (MoCA–DS) and Total Score (MoCA–TS), including the number of patients scoring below the cut–off, before (T1) and after (T2) detoxification.

| MoCA–DS (range) | T1 (*n* = 39) | | T2 (*n* = 39) | |
|---|---|---|---|---|
| | Mean (*SD*) | % | Mean (*SD*) | % |
| Executive & visuospatial functions (0–6) | 4.36 (1.20) | 72.7% | 4.74 (1.17) | 79.0% |
| Attention (0–6) | 5.00 (1.07) | 83.3% | 5.13 (1.08) | 85.5% |
| Language (0–5) | 4.40 (1.05) | 88.0% | 4.66 (0.63) | 92.2% |
| Abstract reasoning (0–2) | 1.63 (0.62) | 81.5% | 1.81 (0.44) | 90.5% |
| Memory (0–5) | 2.94 (1.58) | 58.8% | 3.52 (1.54) | 70.4% |
| Orientation (0–6) | 5.84 (0.48) | 97.3% | 5.79 (0.48) | 96.5% |
| MoCA–TS (0–30) | 24.16 (3.01) | 80.1% | 25.65 (2.78) | 85.5% |
| *n* (%) < 25* | 56.3% | | 30.6% | |

Note: % = proportion correct (mean score divided by maximum domain score times 100%); * = significant difference between T1 and T2 $p < .005$.

***Table 6.2.*** Pearson and Spearman correlations between patient characteristics and the Montreal Cognitive Assessment – Total Score (MoCA–TS) both before (T1) and after (T2) detoxification.

| | MoCA–TS | |
|---|---|---|
| | T1 | T2 |
| Sex | –0.196 | 0.060 |
| Age | 0.089 | 0.101 |
| Number of days used in the past 30 days | –0.013 | 0.003 |
| Daily GHB dose | –0.152 | 0.111 |
| Number of months of daily use | –0.180 | 0.202 |
| Number of months of use in the lifetime | –0.143 | 0.167 |
| GHB exposure score | –0.217 | 0.217 |
| Number of comas experienced | 0.978 | –0.079 |

***Table 6.3.*** Pearson and Spearman correlations between patient characteristics and scoring above or below the Montreal Cognitive Assessment (MoCA) cut–off both before (T1) and after (T2) detoxification.

| | MoCA cut–off | |
|---|---|---|
| | T1 | T2 |
| Sex | 0.222* | –0.171 |
| Age | –0.081 | 0.000 |
| Number of days used in the past 30 days | 0.023 | –0.067 |
| Daily GHB dose | –0.075 | 0.109 |
| Number of months of daily use | 0.020 | –0.093 |
| Number of months of use in the lifetime | 0.129 | –0.192 |
| GHB exposure score | 0.137 | 0.147 |
| Number of comas experienced | 0.979 | –0.079 |

Note: * = $p < .05$.

***Table 6.4.*** Means and standard deviations (*SD*) of the Montreal Cognitive Assessment (MoCA) Domain Scores (MoCA–DS) and Total Score (MoCA–TS), including the number (%) of patients scoring below the cut–off, split per outcome group (non–relapse and relapse) before (T1) and after (T2) detoxification.

| MoCA–DS (range) | T1 | | |
|---|---|---|---|
| | Non–relapse ($n$ = 28) | Relapse ($n$ = 52) | $p$–value |
| Executive & visuospatial functions (0–6) | 4.42 (1.14) | 4.33 (1.24) | .721 |
| Attention (0–6) | 5.32 (0.86) | 4.83 (1.13) | .047* |
| Language (0–5) | 4.46 (1.04) | 4.37 (1.07) | .691 |
| Abstract reasoning (0–2) | 1.57 (0.69) | 1.65 (0.59) | .576 |
| Memory (0–5) | 3.61 (1.42) | 2.58 (1.55) | .005* |
| Orientation (0–6) | 5.82 (0.39) | 5.85 (0.45) | .810 |
| MoCA–TS (0–30) | 25.21 (2.91) | 23.60 (2.94) | .021* |
| $n$ (%) < 25 | 56.6% | 76.9% | .030* |

Note: * = $p < .05$.

Given that only cognitive performance on T1 was related to treatment outcome, these scores were used in the backward logistic regression analyses to explore the predictive value of the MoCA for relapse. The logistic regression model was statistically significant, $\chi^2(1) = 8.62$, $p < .003$, with only MoCA–DS memory as a significant predictor in the final model. The model explained between 10.2% and 14.1% (Nagelkerke $R^2$, depending on which MoCA–DS were included/excluded in the model) of the variance in relapse and correctly classified 68.8% of the cases. Each point scored on MoCA–DS memory at T1 increases the odds of non–relapse with 1.64.

| | T2 | |
|---|---|---|
| Non–relapse ($n$ = 29) | Relapse ($n$ = 33) | $p$–value |
| 4.80 (1.08) | 4.69 (1.26) | .750 |
| 5.27 (1.07) | 5.00 (1.09) | .319 |
| 4.72 (0.59) | 4.61 (0.66) | .463 |
| 1.72 (0.53) | 1.89 (0.33) | .167 |
| 3.83 (1.47) | 3.24(1.58) | .138 |
| 5.83 (0.47) | 5.76 (0.50) | .574 |
| 26.17 (2.24) | 25.21 (2.91) | .163 |
| 27.6% | 42.4% | .171 |

# Discussion

This study investigated cognitive impairment in patients with GUD, and its relationship with GHB use patterns and relapse in GHB use after detoxification. Using the MoCA, a substantial number of patients with GUD screened positive for cognitive impairment before detoxification (56.3%). Cognition improved after detoxification with still about one third screening positive for impairment (30.6%). The cognitive domain showing the strongest impairment was memory. No correlation was found between cognitive impairment and the number of comas, GHB use patterns, or severity of GUD. Cognitive impairment before detoxification, particularly on the subscale memory, was associated with relapse between detoxification and follow–up.

In the current sample, more than half of the included patients had an indication for cognitive impairment during admittance, with a mean MoCA–TS of 24.2. A recent study observed similar to slightly better MoCA scores in patients with substance use disorders including alcohol, cannabis, stimulant and opioids (MoCA–TS: 25.3, 26.3, 25.9, and 24.7 respectively; Bruijnen, Dijkstra, et al., 2019). Though no direct comparison between these two samples can be made, this does raise the question whether the observed cognitive impairments in patients with GUD are specific for excessive GHB use, or related to (indirect) negative effects of substances of abuse on cognitive performance in general. Furthermore, it is important to note that most patients with primary GUD have poly–substance use problems, often stimulants (Dijkstra et al., 2017; Beurmanjer et al., 2019), making it difficult to differentiate between effects of GHB and other substances.

Patients showed a trend towards improvement in MoCA–TS and a significant decrease in scoring below the cut–off between T1 and T2, indicating that cognitive functioning partially recovered during detoxification. This is in line with studies in SUD patients using other sedatives, including alcohol (Wobrock et al., 2009) and benzodiazepines (Ros–Cucurull et al., 2018), who also show improvement of cognitive functioning during abstinence. It is important to note that patients in the current study were only abstinent of GHB for approximately three weeks when T2 was administered. Therefore, further improvement with prolonged abstinence is expected. Literature on alcohol has for instance shown that cognitive function can improve up to after six weeks to over a year of abstinence (Walvoort et al., 2013). Future studies should further investigate recovery of cognitive impairment in patients with GUD with long–term abstinence.

Patients with GUD scored particularly low on the domain memory, also when compared to studies in patients with other SUD (Bruijnen, Dijkstra, et al., 2019). Since GHB receptors are predominantly expressed in the hippocampus, this observation might reflect the direct

effects of GHB in the brain (Xie & Smart, 1992; Castelli et al., 2000; Carter et al., 2009). GHB–induced comas have also been suggested to affect hippocampal activity, both in humans (Raposo Pereira et al., 2018a) and animals (Johansson et al., 2014), which could also contribute to the observed memory problems. Since memory is a broad concept, with various sub domains (e.g. working memory, long–term memory, declarative memory, etc), future studies should explore which specific memory domains are most affected in patients with GUD.

Despite several studies suggesting that cognitive impairment in patients with GUD might be caused by GHB–induced comas (Raposo Pereira et al., 2018b) the current study did not observe a relationship between the number of self–reported GHB–induced comas and cognitive impairment. Several methodological limitations hamper strong conclusions concerning the (causal) relationship between GHB–induced coma and cognitive impairment. First, studies, including ours, commonly rely on self–reported comas where a clear definition of what constitutes a coma (or if a coma is for instance a short blackout) is lacking. A detailed and reliable account of the total number of GHB–induced comas is therefore hard to obtain. But also due to comas usually occurring on a daily basis (Beurmanjer et al., 2019), amnesia as this might be an aspect of GHB–induced coma itself (Sumnall et al., 2008), and the observed memory impairment in patients with GUD. Second, as seen in other samples, patients with GUD often also use other substances. These might also contribute to cognitive impairment in these patients. Finally, it may also be that it is not the number of GHB–induced comas or substance use levels that contribute to cognitive impairment. Similar to patients with other SUD (Bruijnen, Dijkstra, et al., 2019) our data did not find a relationship between cognitive performance on the MoCA and years of regular use, dose, severity of dependence and comas. This suggests that other factors might be involved, for instance lack of sleep, malnutrition or other psychiatric or somatic comorbidities. Future studies should explore mechanisms contributing to cognitive impairment in patients with GUD and other SUD.

The current study shows that MoCA performance, in particular on the memory domain, were associated with the risk of relapse. This is in line with studies in other SUD, such as alcohol (Czapla et al., 2015), cocaine (Turner et al., 2009) and opioids (Ma et al., 2019), where cognitive impairment is associated with the risk of relapse and poor treatment retention. Cognitive functions are crucial to direct behaviour and obtain control over impulses and emotions (Loughead et al., 2015), including substance use. Cognitive impairment in patients with SUD (including GUD) might thus interfere with taking control of substance use, to change behaviour, and reach treatment goals (Stevens et al., 2014; Loughead et al., 2015). SUD patients with cognitive impairment might require treatment adaptations focussing on cognitive enhancement (Verdejo–García, 2016; Rensen et al., 2019). Indeed, several studies

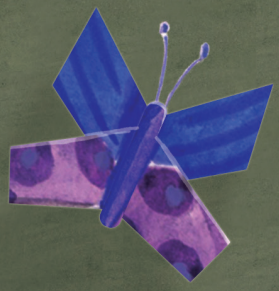
have shown that such personalized treatment approaches can be efficacious in patients with SUD and cognitive impairment (Eack et al., 2016). To what extent this might also benefit patients with GUD remains to be studied.

The results of this study should be viewed in the light of several limitations. First, the MoCA is not a diagnostic tool for cognitive impairment. While the MoCA has been shown to be a valid screening instrument in patients with SUD (Bruijnen, Jansen, et al., 2019), no extensive neuropsychological assessment was used in the current study. Therefore, future studies should confirm the current findings, using more detailed neuropsychological assessment across different cognitive domains. Another limitation is that most patients with primary GUD have poly substance use, often stimulants (Dijkstra et al., 2017; Beurmanjer et al., 2019). It is therefore impossible to disentangle GHB effects on cognitive impairment from the effects of other substances. In addition, the observed persistent cognitive impairments could have been present before the use of GHB (or other substances) started. As a result, no causal inferences can be made on the relationships between GHB use/GUD and cognitive impairment in the current study.

In conclusion, in the current study about half of all included patients with GUD had an indication for cognitive impairment before detoxification, decreasing to about one third after detoxification. Cognitive impairment before detoxification, particularly memory problems, were associated with a higher relapse risk after detoxification. Current findings warrant clinical attention for cognitive impairment in patients with GUD, for instance by screening for cognitive impairment using the MoCA, and full neuropsychological assessment after a sufficient period of abstinence following detoxification where appropriate. Future studies should confirm these findings and explore whether GUD patients with cognitive impairment require specific treatment adaptations.

Lieve Yori en Mark, mijn studiegenootje. We hebben elkaar leren kennen tijdens het onderzoeksblok in het tweede jaar in Maastricht, het klikte meteen! Nu, inmiddels al 15 jaar later, zijn we nog steeds vriendinnen. Wie had gedacht dat we nu beiden gepromoveerd zouden zijn, getrouwd en kinderen hebben? Het wordt bijna een cliché, maar hopelijk kunnen we elkaar vanaf nu weer wat vaker zien, je bent belangrijk voor me! Zal ik de volgende keer weer koken?

Lieve Sanne en Ruud, ik ben blij jullie onze vrienden te mogen noemen. Wat heerlijk dat de kinderen het ook nog eens goed met elkaar kunnen vinden. Ik had vijf jaar geleden niet gedacht dat we in zo'n korte tijd zo'n goede vrienden zouden worden. Voor jullie hebben we altijd tijd gehad, het gemak van in de buurt wonen wellicht? Wat het ook is, ik hoop dat dit nooit verandert!



# Chapter 7

## Summary and general discussion

# Summary and general discussion

Chronic substance (ab)use has acute and long–term effects on cognitive functioning. The presence of substance–induced NCD also affects the course and results of treatment. For instance, having NCD is predictive of higher drop–out rates during treatment and less reported abstinence. However, patients and clinicians are not always aware of these cognitive deficits, and subjective reports of cognitive complaints do not correlate well with the actual cognitive test performance. This illustrates that it is important to diagnose substance–induced NCD using performance–based neuropsychological testing. As administering an NPA in all patients entering addiction treatment is not feasible, because it is time consuming, relatively expensive and needs highly experienced clinicians and motivation from the patient, there is need for shorter instruments to measure cognitive (dys)function in patients with SUD. Such a cognitive screening instrument should meet certain criteria, for instance, it should have a short administration time, have an easy to interpret score and be relatively independent of education, language or culture. It should have good psychometric properties like test–retest and inter–rater reliability, and good concurrent and predictive validity with high levels of sensitivity and specificity. Above all, it must be easy to score and be acceptable in administration for both the clinician and the patient. A potentially promising cognitive screening instrument for detecting substance–induced NCD is the MoCA.

The main objective of this thesis was to investigate if the MoCA is indeed a feasible and valid cognitive screening instrument that can bridge the aforementioned gap between knowledge – exactly knowing what needs to be done to plan well indicated treatment – and clinical reality – realizing an NPA for each individual is impossible. In this chapter, I will present and discuss the main findings and their clinical implications, starting with the psychometric properties of the MoCA. Next, findings on the applicability of the MoCA in addiction health care will be discussed, followed by the prevalence and course of NCD in addiction health care. Finally, I will discuss the strengths and limitations, clinical considerations and provide guidelines for future research.

### *Psychometric properties of the Montreal Cognitive Assessment*

*Reliability*

A cognitive screening instrument should have excellent reliability, which is the overall consistency of a measure, meaning that it should produce similar results under consistent conditions. There are several forms of reliability. In Chapter 2 both alternate–form and test–retest reliability of all three Dutch translations of the MoCA were examined in a sample of 210 healthy participants aged 18–70. Regarding the alternate–form reliability, all three versions of de MoCA were found to be largely equivalent, based on MoCA–TS and –MIS.

This replicated the findings of Chertkow et al. (2011) and Nasreddine et al. (2016) using the English and French–language versions of the MoCA in older adults. At the level of individual items, however, small but systematic differences were found for the items animal naming, sentence repetition and abstract reasoning, mostly in favour of the alternate forms except for sentence repetition where MoCA version 7.1 had significantly higher scores. Similar findings were reported by Lebedeva et al. (2016) for both the items animal naming and abstract reasoning. In addition, they also found a performance difference for the item figure copy across the different versions. The fact that this was currently not found could be explained by the thorough checking of scores and the conservative scoring method that was used, thereby eliminating ambiguities in scoring and possible inter–rater differences as previously reported by Cumming et al. (2020). In a sample of 82 patients with SUD, significant differences in performance between MoCA versions 7.1 and 7.2 were found on all MoCA–DS except abstract reasoning, memory and orientation (Chapter 3). Also, mean scores on all MoCA–DS except language, were higher on MoCA version 7.2 as compared to version 7.1. This can, however, be interpreted by a non–specific practice effect as the versions were administered in a fixed order.

For test–retest reliability good to excellent results were found in Chapter 2 for MoCA–TS between versions 7.1–7.2 (ICC = 0.64) and 7.1–7.3 (ICC = 0.82). This is in line with findings of other studies (Costa et al., 2012; Feeney et al., 2016; Nasreddine et al., 2016; Kopecek, Bezdicek, et al., 2017; Wu et al., 2017). These test–retest reliabilities can be used to compute Reliable Change Indices (RCI; Chelune et al., 1993) making the MoCA–TS useful for monitoring change over time. The MoCA–MIS, on the other hand, had poor to fair test–retest reliabilities (7.1–7.2: ICC = 0.32; 7.1–7.3: ICC = 0.48), possibly due to a strong negative skewness of scores with ceiling performances in many of the cognitively unimpaired participants on both versions. In cognitively impaired individuals, the MoCA–MIS has been found to be a useful index of monitoring change over time, making it a good predictor, for example, for conversion from mild cognitive impairment to Alzheimer's disease (Julayanont et al., 2014).

*Validity*

In addition to reliability, the validity of an instrument is also very important. In psychometrics, test validity is the extent to which an instrument is generalizable to the real world. There are many different types of validity, probably the most important being construct validity: does a test measure what it is supposed to measure? In other words, does the MoCA actually assess cognitive functioning in the domains it claims to measure? Construct validity is usually determined by comparing results on a test to results on a conceptually similar test. In Chapter 3, results on the MoCA were compared to results on an NPA that was composed on the basis of the cognitive domains that the MoCA is said to measure. It was found that results on all MoCA–DS

correlated significantly to results on the corresponding NPA domain when administered subsequently (correlation coefficients ranging from small [.229] to medium [.542]), providing evidence for low to moderate construct validity of the MoCA for use in addiction care.

Another important form of validity is criterion validity, which is the extent to which the result of a test is related to an outcome (criteria). In other words, how well do results on the MoCA correspond to the classification of cognitive impairments based on an NPA? Criterion validity can be determined concurrently, by administering the MoCA and an NPA on the same day, and predictively, by administering the MoCA several days/weeks previous to an NPA. On both instances, the validity is determined by calculating at several possible MoCA cut–off points: the sensitivity (the percentage of patients with NCD who scored below the cut–off score on the MoCA) and specificity (the percentage of patients without NCD who scored above the cut–off score on the MoCA), by which the adequacy of the screening test is being determined. But also by calculating at the same cut–off points: the positive predictive value (PPV; the percentage of patients scoring below the cut–off on the MoCA who actually have NCD), and the negative predictive value (NPV; the percentage of patients scoring above the cut–off on the MoCA who actually do not have NCD), by which the patient is being assessed.

In Chapter 3, this was done in a heterogeneous sample of 82 patients with SUD. Predictively, a MoCA–TS cut–off score of 24 yielded the most optimal sensitivity (55.6%), specificity (62.2%), PPV (64.1%) and NPV (53.5%). Concurrently, a MoCA–TS cut–off score of 25 yielded the most optimal sensitivity (66.7%), specificity (73.0%), PPV (75.0%) and NPV (64.3%). These findings are partly in line with other MoCA studies, which have some important differences to the current study. Firstly, only homogeneous groups of patients with AUD were included in those studies (as opposed to a heterogeneous group of patients with SUD), limiting their external validity (Wester et al., 2013; Oudman et al., 2014; Alarcon et al., 2015). Secondly, patients in these earlier studies were abstinent for only one week (Alarcon et al., 2015) or for more than six months (Oudman et al., 2014), while in clinical practice patients are often not abstinent at intake. One study that also related MoCA performance directly to an NPA (Ewert et al., 2018) found a higher cut–off score in a sample of hospitalized patients with AUD. The first–known study on the MoCA, performed in a heterogeneous group of patients with SUD, found slightly better psychometric properties than were currently found, but were most in line with the present findings (Copersino et al., 2009).

***Applicability of the Montreal Cognitive Assessment in addiction health care***

Although it has often been argued that performance on cognitive screening instruments should not be affected by demographic variables, in practice such effects have been reported for many cognitive instruments. Therefore, it is important to examine the influence of demographic variables, making it possible to take them into consideration when interpreting results.

*Effect of demographic variables*

The MoCA takes the effect of years of education into account to some extent, by awarding an additional point to the MoCA–TS for those with twelve years of education or less. There is some evidence that other demographic variables also affect MoCA performance, but these have not been extensively studied for individuals under 65. Therefore, the effects of demographic variables age, sex, level of education and estimated premorbid intelligence on MoCA performance were investigated in healthy participants (Chapter 2) and in patients with SUD (Chapters 3 and 4).

Regarding age, it was found both for healthy participants and for patients with SUD (specifically alcohol and cannabis) that older individuals performed worse on the MoCA–TS than younger participants. In healthy participants this was also found for the MoCA–MIS. Comparing these results to other studies shows that they are in agreement with previous findings in patients with AUD aged 18 and older (Alarcon et al., 2015), in a sample of healthy controls aged 25–91 (Freitas et al., 2012), and in several samples of adults aged 50 and older (Zheng et al., 2012; Malek–Ahmadi et al., 2015; Oren et al., 2015). Originally, however, Nasreddine et al. (2005) did not find an effect of age in a sample of geriatric patients aged 55–85, possibly due to the small age range. Strikingly, a positive correlation was found between age and the MoCA–TS for patients using stimulants (Chapter 4). This may be a consequence of the primarily enhancing effects of stimulant intoxication at low doses (Scott et al., 2007; Spronk et al., 2013).

Regarding sex, it was found that women outperformed men on the MoCA–MIS, but no sex differences were found on MoCA–TS. The difference between men and women has been objectified in episodic memory functioning in childhood ages (Gur et al., 2012) and in particular working memory tasks in adults (Saylik et al., 2018). In other studies regarding the MoCA, only one study also found a significant, but small sex difference on the delayed recall item in Spanish participants aged 18 and older (Ojeda et al., 2016). Due to the small effect size, an adjustment for sex is not needed.

An adjustment for the number of years of education is already implemented in the MoCA (Nasreddine et al., 2005). However, this adjustment method may not be optimal for the Dutch educational system in which level of education is a more important factor for educational attainment than the number of years of formal education (Duits et al., 2014). Therefore, the existing adjustment for years of education may not be optimal. It was found in healthy participants that performance on the MoCA is moderated by both level of education and estimated premorbid intelligence (Chapter 2), therefore, a more fine–grained adjustment for level of education is introduced in Chapter 3, in which one additional point is awarded for individuals with an average level of education and two points for individuals with a low level of education, providing a more robust solution to overcome the moderation effect of level of education. The effect of intelligence on MoCA performance was expected, as it is known that intelligence typically correlates highly with level of education in young and middle–aged adults (Lezak et al., 2012) and the effect of years of education was already demonstrated previously (Nasreddine et al., 2005; Zheng et al., 2012; Sugarman et al., 2014; Yancar Demir et al., 2015; Apolinario et al., 2018).

*Effect of substance use related characteristics*

The effect(s) of several substance–related characteristics (i.e. substance type, abstinence duration, years of regular use, polysubstance use, severity of the substance use and psychological complaints such as depressive symptoms, anxiety and stress) were also examined. Neither substance type nor abstinence duration were significant predictors of performance differences on the MoCA (Chapter 3). It should be noted, however, that the effect of age on MoCA performance was significant for patients using alcohol and cannabis, but not for other substances of abuse. Next, no relation was found between MoCA performance and any of the substance use related characteristics: years of regular use, polysubstance use, being abstinent, abstinence duration, severity of the dependence and/or abuse, and psychological complaints (depressive symptoms, anxiety, or stress). Also, in a group of patients with GUD, no relationship was found between MoCA performance and severity of GHB use (Chapter 6). The lack of relations between the MoCA–TS and psychological complaints is in line with recent findings in a sample of polysubstance users showing that the MoCA–TS was unrelated to the results on a (psychiatric) symptom checklist (Hagen et al., 2019). As for being abstinent or not, and abstinence duration, Walvoort et al. (2013) argued that a minimum period of six weeks abstinence is recommended before the intoxicating effects of alcohol in the brain are minimised and an NPA can be administered validly. However, the MoCA is a cognitive screener that may be less sensitive to the (sub) acute effects of substance use than an NPA. Furthermore, our current sample did not only consist of alcohol users.

***Prevalence and course of neurocognitive disorders in addiction health care***

Now that some important psychometric properties of the MoCA and the effects of several (demographic/substance use related) characteristics on MoCA performance are known, the next step is to further explore the prevalence and course of cognitive impairments in addiction health care.

*Prevalence of neurocognitive disorders*

Previous research pointed to an estimated prevalence of cognitive impairments in patients with SUD ranging from 30% – 80% (Copersino et al., 2009). We found a prevalence of substance–induced NCD of 31% within addiction care facilities, falling at the bottom of the estimated range. Differences in prevalence between substances were not as profound as was expected (alcohol = 34%, cannabis = 21%, stimulants = 27% and opioids = 38%). This could, however, be influenced by the high percentage of polysubstance users in our sample. In Chapter 6, a higher prevalence of cognitive impairments of 56% was found in patients referred to a detoxification unit for their GHB dependence, a group in which polysubstance use is also not uncommon (Dijkstra et al., 2017).

*Course of neurocognitive disorders during treatment*

Given the adequate test–retest reliability and the availability of parallel versions, the MoCA can potentially be used to follow the course of cognitive performance over time in patients with SUD. This was examined in Chapter 5, in a sample of 524 patients with AUD who were clinically admitted to the Centre of Excellence for Korsakoff and Alcohol–Related Cognitive Disorders, and in Chapter 6 in a sample of 103 patients entering detoxification treatment for GHB. In Chapter 5, significant differences were found in cognitive performance between three groups of patients with AUD, where patients with KS performed lowest, followed by patients with ARCI and those with AUD only, respectively. Cognitive performance improved in all three groups between intake and the sixth week of clinical admission, with a further improvement up to clinical discharge. With this, we found that all patients with AUD seem to benefit from prolonged clinical treatment. In Chapter 6, an improvement of cognitive performance on the MoCA was also found in patients with GUD, when measured before and after detoxification. When examining the MoCA–DS, patients with KS did not change on the memory domain, while patients with ARCI improved over all three assessments. In patients with GUD, the MoCA–DS memory and attention seemed to be indicative for a higher risk of relapse.

Self–reported and clinician–observed everyday cognitive functioning was also measured in Chapter 5. It was found that patient ratings were higher than clinician ratings, and that patient ratings did not differ between groups, where the clinician ratings did. This finding is in line with the literature in which patients do not always report subjective complaints because of a lack of insight into their own cognitive deficits (Walvoort et al., 2016). On the contrary, patients reported a significant improvement in everyday cognitive functioning, where the clinicians do not report significant changes. This may be influenced by the fact that patients were probably in a better emotional state when completing the final assessment, as they were abstinent and (soon to be) clinically discharged. The changes in cognitive performance were related to changes in everyday cognitive functioning, albeit with only small to medium effect sizes. This supports the literature that cognitive performance on objective measures does not predict cognitive impairments in the absence of subjective experiences of everyday cognitive problems (Horner et al., 1999).

***Strengths and limitations***

Each study had its own strengths and limitations, as described in detail at the end of the chapters. There are also some general remarks to be made taking all studies together. This research project found its origin in clinical practice, where several esteemed colleagues put their hands and minds together to formulate a plan to close a gap. This collaboration between addiction health care centres resulted in a multicentre project where large groups of patients could be included. There is an important note when interpreting our findings, specifically those regarding the prevalence of substance–induced NCD. As stated in the introduction, the number of patients entering addiction health care are likely only the tip of the 'users'–iceberg. Epidemiologically, it is unknown what substance users that do not enter treatment use and if they have cognitive impairments or not. Also, as the predictive and concurrent validity of the MoCA were found to be low to moderate, the actual prevalence of substance–induced NCD may well be different than that currently found. However, as a result of well characterising our groups of patients in terms of which drugs they used, how much of it and for how long, they are representative for the population of substance (ab)users, making results highly generalisable. It is always the question (as also stated above regarding cognitive complaints) to what extent substance use can be objectively measured via self–report. We aimed to overcome this question by using a validated and evidence–based interview for relevant patient characteristics in addiction health care: the MATE (Schippers et al., 2011).

***Clinical consideration***

Now, at the end of this project availability of the MoCA has risen to over 100 languages in 60 countries. The test has been under constant development, as there are different forms available, for instance for telephone screening or blind subjects, but also an app version is now available. Research regarding the MoCA is rapidly expanding. Where only a few studies had investigated usability and feasibility of the MoCA in addiction care at the start of my PhD project, the amount of published papers on this subject has gradually grown, and is still growing since then.

The MoCA does not conform to the criteria of an ideal cognitive screening instrument, as performance is not independent of age, educational level, premorbid intelligence and substance type. Therefore, more elaborate stratified or regression–based normative data should be constructed, adjusting for influences of age, education and intelligence. Nevertheless, the MoCA is a cognitive screening instrument and not a diagnostic measure. Thus, even if a screener has excellent sensitivity and specificity, an NPA remains the gold standard for diagnostic purposes, as well as for the specification of specific cognitive profiles.

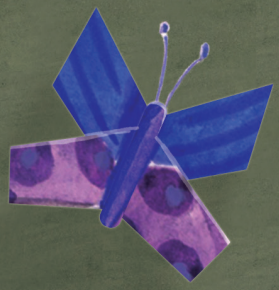
During the course of this project, we found that awareness of cognitive impairments (NCD) in addiction health care has grown, and is still growing. See, for instance, the recently published comprehensive textbook by Verdejo–García (Cognition and addiction: a researcher's guide from mechanisms towards interventions; 2020). When using the MoCA to screen for cognitive impairments in addiction care, it is important to take age, educational level and substance type into account when interpreting results. The MoCA–TS and MoCA–MIS are the most reliable and valid scores, where the other MoCA–DS are not. If one does look at MoCA–DS, low scores on the memory domain seem to be predictive of alcohol–induced NCD, where no improvement over time further seems to indicate a major alcohol–induced NCD. The MoCA can also be used to monitor cognitive performance during the course of treatment, with an improvement in cognitive performance seen in the first six weeks of clinical admission, but also further during treatment.

One should always be aware of the sensitivity and specificity at several cut–off scores. If you do not want to miss a patient with cognitive impairments, consider raising the cut–off score prior to assessment, while a lower predetermined cut–off lowers the chance of falsely indicating impairments when none exist. The confirmed lack of illness insight into cognitive functioning also states the importance of screening at an early stage of health care, so that results can help in appropriate decision making.

***To conclude...***

The MoCA is not the 'ideal screener' we were searching for, but at this point it is rather good second best. If an ideal screening tool exists, what should it look like? Are there other promising up–and–coming cognitive screening instruments? Or has the better and improved MoCA version 8 already overcome the shortcomings described in this thesis? So far, the MoCA does has some clear advantages and is the best we have. It has already found its way into the Dutch addiction health care centres, and awareness into the cognitive consequences of chronic substance use has risen over the past years. These are very important steps on our way to further reduce the societal impact of SUD and to plan well indicated treatment.

Beter een goede buur dan een verre vriend zeggen ze. Nou! Wij zijn gezegend met allemaal. Joan en Jan, Joost en Trudy, Bart en Ali, bedankt dat jullie altijd een oogje in het zeil houden, dat de koffie altijd klaar staat en het praatje nooit ongelegen komt. Bedankt ook voor jullie interesse, de gezelligheid en de steun ook in moeilijke tijden. Bedankt!



# Appendix

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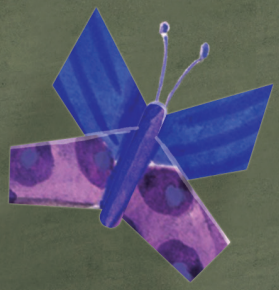


# Appendix

## Samenvatting en algemene discussie

# Samenvatting en algemene discussie

Langdurig chronisch middelengebruik kan zowel op de korte als op de lange termijn nadelige effecten hebben op het cognitief functioneren. De aanwezigheid van neurocognitieve stoornissen (NCS) door een middel heeft invloed op behandelverloop en –resultaten. Zo zijn NCS bijvoorbeeld voorspellend voor een hogere drop–out gedurende de behandeling en is er sprake van minder (gerapporteerde) abstinentie. Zowel de patiënt als de clinicus zijn zich echter niet altijd bewust van deze cognitieve tekorten en subjectieve rapportages van cognitieve klachten correleren niet met cognitieve prestaties op bijvoorbeeld testinstrumenten. Dit illustreert hoe belangrijk het is om NCS te diagnosticeren, gebruikmakend van neuropsychologisch onderzoek (NPO). Het is niet haalbaar om een NPO af te nemen bij alle patiënten die zich in de verslavingszorg aanmelden, omdat het veel tijd kost, relatief duur is en hooggekwalificeerde professionals vereist, maar ook motivatie van de patiënt. Daarom hebben we kortere instrumenten nodig die cognitief (dis) functioneren bij patiënten met een verslaving kunnen meten. Een dergelijke cognitieve screener moet aan bepaalde criteria voldoen. Zo moet hij bijvoorbeeld snel af te nemen zijn en makkelijk te interpreteren. Hij moet daarnaast relatief onafhankelijk zijn van invloeden van opleiding, taal of cultuur. De psychometrische eigenschappen moeten goed zijn, zoals bijvoorbeeld test–hertest– en tussen–beoordelaarbetrouwbaarheid en een goede validiteit met hoge gevoeligheid en specificiteit. Bovenal moet een dergelijke screener makkelijk te scoren zijn en zowel voor de clinicus als voor de patiënt makkelijk af te nemen. Een veelbelovende cognitieve screener voor het opsporen van NCS is de Montreal Cognitive Assessment (MoCA).

Het hoofddoel van dit proefschrift was om te onderzoeken of de MoCA inderdaad een bruikbaar en valide screeningsinstrument is dat de eerdergenoemde kloof tussen kennis – kennis van wat nodig is om goed geïndiceerde behandeling te kunnen plannen – en klinische realiteit – realisatie dat een NPO voor iedereen onmogelijk is – kan overbruggen. In deze samenvatting zullen de belangrijkste resultaten en de daarbij behorende klinische implicaties gepresenteerd en bediscussieerd worden, startend met de psychometrische eigenschappen van de MoCA. Vervolgens komen de resultaten betreffende de inzet van de MoCA in de verslavingszorg aan bod gevolgd door de prevalentie van NCS binnen de verslavingszorg en het behandelverloop. Tot slot zal worden ingaan op de sterktes en beperkingen van het onderzoek, klinische overwegingen van de resultaten en zullen richtlijnen voor toekomstig onderzoek gegeven worden.

***Psychometrische eigenschappen van de Montreal Cognitive Assessment***

*Betrouwbaarheid*

Betrouwbaarheid is de algemene samenhang, of coherentie, van een meetinstrument, dit wil zeggen dat verschillende afnames onder gelijkblijvende omstandigheden dezelfde resultaten moet en geven. Er zijn verschillende vormen van betrouwbaarheid. Een cognitieve screener moet uitstekende betrouwbaarheid hebben. In Hoofdstuk 2 werden zowel de parallelle–versie– en test–hertestbetrouwbaarheid van alle drie de Nederlandse versies van de MoCA onderzocht in een groep van 210 gezonde participanten tussen 18–70 jaar. Betreffende de parallelle–versiebetrouwbaarheid, waren alle drie de versies van de MoCA grotendeels equivalent, gekeken naar de MoCA–TS en –MIS. Dit bevestigde eerdere bevindingen van Chertkow et al. (2011) en Nasreddine et al. (2016) waarbij de Engels– en Franstalige versies van de MoCA waren onderzocht bij oudere volwassenen. Op het niveau van de individuele items werden echter kleine, maar systematische verschillen gevonden voor de items dieren benoemen, zinnen nazeggen en abstractievermogen. Deze waren doorgaans in het voordeel van de alternatieve versies. Behalve zinnen nazeggen, waarbij op MoCA versie 7.1 significant hogere scores behaald werden dan op de andere versies. Vergelijkbare bevindingen werden gerapporteerd door Lebedeva et al. (2016) voor zowel de items dieren benoemen als abstractievermogen. Zij vonden echter ook een prestatieverschil voor het item figuur natekenen over de verschillende versies. Het feit dat dit in het huidig onderzoek niet gevonden werd kan verklaard worden door het uitvoerig nakijken van de scores en de conservatieve scoringsmethode die gebruikt is, waardoor onduidelijkheden in scoring en mogelijk tussen–beoordelaarsverschillen, zoals eerder gerapporteerd door Cumming et al. (2020), tot een minimum beperkt zijn gebleven. In een groep van 82 patiënten met een verslaving werden significante verschillen in scores tussen MoCA versie 7.1 en 7.2 gevonden op alle MoCA–DS behalve abstractievermogen, geheugen en oriëntatie (Hoofdstuk 3). Gemiddelde scores op alle MoCA–DS behalve taal waren hoger op MoCA versie 7.2 vergeleken met versie 7.1. Deze bevindingen kunnen echter geïnterpreteerd worden door een niet–specifiek leereffect, gezien de versies in een vaste volgorde werden afgenomen.

Voor de test–hertestbetrouwbaarheid werden goede tot uitstekende resultaten gevonden in Hoofdstuk 2, betreffende de MoCA–TS tussen versies 7.1–7.2 (ICC = 0.64) en 7.1–7.3 (ICC = 0.82). Dit is vergelijkbaar met bevindingen van andere onderzoeken (Costa et al., 2012; Feeney et al., 2016; Nasreddine et al., 2016; Kopecek, Bezdicek, et al., 2017; Wu et al., 2017). De gevonden test–hertestbetrouwbaarheden kunnen gebruikt worden om zogenaamde Reliable Change Indices (RCI; Chelune et al., 1993) te berekenen: een maat waarmee de significantie van een verandering betrouwbaar berekend kan worden. Dit maakt de MoCA–TS geschikt om veranderingen over tijd te meten. De MoCA–MIS daarentegen had slechte tot matige test–hertestbetrouwbaarheden (7.1–7.2: ICC = 0.32; 7.1–7.3: ICC = 0.48), mogelijk

veroorzaakt door een sterke negatieve scheefheid van de scoreverdeling waarbij velen van de cognitief intacte participanten maximaal scoorden op beide versies. In cognitief beperkte individuen is reeds bewezen dat de MoCA–MIS een bruikbare index is voor het meten van verandering over tijd, wat de maat een goede voorspeller maakt voor bijvoorbeeld de overgang van lichte cognitieve stoornissen naar de ziekte van Alzheimer (Julayanont et al., 2014).

*Validiteit*

Naast betrouwbaarheid, is de validiteit van een instrument ook zeer belangrijk. Testvaliditeit is de mate waarin de uitkomsten op een instrument te generaliseren zijn naar uitkomsten uit de echte wereld. Er zijn vele verschillende vormen van validiteit, waarvan constructvaliditeit waarschijnlijk de belangrijkste is. Constructvaliditeit wil zeggen: meet een test wat hij beoogt te meten? Met andere woorden, meet de MoCA daadwerkelijk cognitief functioneren in de domeinen die hij beoogt te meten? Constructvaliditeit wordt meestal bepaald door de resultaten op een test te vergelijken met resultaten op een conceptueel vergelijkbare test. In Hoofdstuk 3 zijn de resultaten op de MoCA vergeleken met resultaten op een NPO dat was samengesteld op basis van de cognitieve domeinen die de MoCA beoogt te meten. De resultaten toonden aan dat alle MoCA–DS significant samenhingen met de resultaten op het corresponderende NPO domein, wanneer beiden achter elkaar waren afgenomen (correlatiecoëfficiënten varieerden van laag [.229] tot matig [.542]), wat bewijs geeft voor lage tot matige constructvaliditeit van de MoCA voor gebruik in de verslavingszorg.

Een andere belangrijke vorm van validiteit is de criteriumvaliditeit. Dit is de mate waarin het resultaat van een test gerelateerd is aan een uitkomst (criterium). Met andere woorden, hoe goed corresponderen de resultaten op de MoCA met de classificatie van cognitieve beperkingen gebaseerd op een NPO? Criteriumvaliditeit kan gelijktijdig (*concurrently*) bepaald worden, door de MoCA en het NPO op dezelfde dag af te nemen, en voorspellend (*predictively*), door de MoCA enkele dagen/weken voor een NPO af te nemen. In beide gevallen wordt de validiteit bepaald door op verschillende mogelijke afkapwaarden van de MoCA de sensitiviteit (het percentage van de patiënten met NCS, die onder de afkapwaarde van de MoCA scoren) en de specificiteit (het percentage van de patiënten zonder NCS, die boven de afkapwaarde van de MoCA scoren) te berekenen, waarmee de accuratesse van de screener wordt beoordeeld. Tegelijk worden met dezelfde afkapwaarden de positief voorspellende waarde (PVW: het percentage van de patiënten die onder de afkapwaarde scoren op de MoCA, die ook NCS hebben), en de negatief voorspellende waarde (NVW: het percentage van de patiënten die boven de afkapwaarde scoren op de MoCA, die geen NCS hebben) berekend, waarmee de patiënt wordt beoordeeld.

In Hoofdstuk 3 werd dit gedaan in een heterogene groep van 82 patiënten met een verslaving. Voorspellend (*predictively*) werd een MoCA–TS–afkapwaarde van 24 gevonden die de meest optimale sensitiviteit, specificiteit, PVW en NVW opleverde. Gelijktijdig (*concurrently*) werd een MoCA–TS–afkapwaarde van 25 gevonden die de meest optimale waarden opleverde. Deze resultaten komen deels overeen met andere MoCA–studies, welke belangrijke verschillen laten zien met het huidige onderzoek. Ten eerste werden homogene groepen van patiënten met een alcoholverslaving in deze studies geïncludeerd (in tegenstelling tot een heterogene groep patiënten met verslaving aan verschillende middelen), wat hun externe validiteit beperkt (Wester et al., 2013; Oudman et al., 2014; Alarcon et al., 2015). Ten tweede waren de patiënten in de eerdere onderzoeken slechts één week abstinent (Alarcon et al., 2015) of juist meer dan zes maanden (Oudman et al., 2014), terwijl het in de klinische praktijk zeer vaak voorkomt dat een patiënt niet abstinent (of zelfs onder invloed) is tijdens de intake. Er is één onderzoek dat prestaties op de MoCA ook direct vergeleek met een NPO (Ewert et al., 2018), zij vonden een hogere afkapwaarde in een groep opgenomen patiënten met een alcoholverslaving. In het eerst bekende onderzoek met de MoCA, uitgevoerd in een heterogene groep patiënten met verslaving werden net iets betere psychometrische eigenschappen gevonden dan in het huidige onderzoek. Deze resultaten kwamen het meest in de buurt van de huidige resultaten (Copersino et al., 2009).

***Toepasbaarheid van de Montreal Cognitive Assessment in de verslavingszorg***

Hoewel vaak wordt beargumenteerd dat prestaties op een cognitieve screener niet beïnvloed mogen worden door demografische eigenschappen (zoals leeftijd, geslacht, opleiding), worden in de praktijk zulke effecten gevonden voor vele cognitieve instrumenten. Daarom is het belangrijk om deze invloeden te onderzoeken, wat het mogelijk maakt deze in overweging te nemen bij het interpreteren van resultaten.

*Invloed van demografische eigenschappen*

Tot op zekere hoogte wordt het effect van aantal jaren opleiding bij de MoCA in acht genomen, door een extra punt toe te kennen aan de MoCA–TS voor diegenen die twaalf jaar of minder aan opleiding hebben genoten. Er is bewijs dat andere demografische eigenschappen ook de prestaties op de MoCA beïnvloeden, maar dit is nog niet uitgebreid onderzocht bij individuen onder de 65 jaar. Daarom werd de invloed van de demografische eigenschappen leeftijd, geslacht, opleidingsniveau en geschatte premorbide intelligentie op de MoCA onderzocht in gezonde individuen (Hoofdstuk 2) en in patiënten met een verslaving (Hoofdstuk 3 en 4).

Betreffende leeftijd werd zowel voor de gezonde individuen als voor patiënten met alcohol– of cannabisverslaving gevonden dat oudere individuen slechter presteerden op de MoCA–TS dan jongere individuen. Bij gezonde individuen werd dit ook gevonden voor de MoCA–MIS. Wanneer deze resultaten vergeleken worden met andere onderzoeken, vinden we overeenstemming met bevindingen in een groep patiënten met alcoholverslaving van 18 jaar en ouder (Alarcon et al., 2015), in een groep gezonde controles tussen 25 en 91 jaar (Freitas et al., 2012) en in verschillende groepen volwassenen van 50 jaar en ouder (Zheng et al., 2012; Malek–Ahmadi et al., 2015; Oren et al., 2015). Nasreddine et al (2005) vond bij de ontwikkeling van de MoCA geen invloed van leeftijd in een groep geriatrische patiënten tussen 55 en 85 jaar. Dit wordt mogelijk verklaard door de kleine leeftijdsrange. Wat opviel was een positieve correlatie tussen leeftijd en MoCA–TS voor patiënten die stimulantia gebruikten (Hoofdstuk 4), wat mogelijk het gevolg is van de primair verhogende effecten van stimulantia–intoxicatie bij lage doseringen (Scott et al., 2007; Spronk et al., 2013).

Betreffende geslacht werd gevonden dat vrouwen hoger scoorden dan mannen op de MoCA–MIS, waar geen verschillen werden gevonden op de MoCA–TS. Het verschil tussen mannen en vrouwen werd reeds geobjectiveerd in het episodisch geheugen in de kinderleeftijd (Gur et al., 2012) en in bepaalde werkgeheugentaken bij volwassenen (Saylik et al., 2018). In andere onderzoeken naar de MoCA was er slechts één onderzoek wat ook een significant, maar klein verschil vond op de uitgestelde herinnering tussen Spaanse mannen en vrouwen in de leeftijd van 18 jaar en ouder (Ojeda et al., 2016). Vanwege de kleine effectgrootte is een correctie voor geslacht op de MoCA niet nodig.

Een correctie voor het aantal jaren opleiding wordt reeds toegepast in de MoCA (Nasreddine et al., 2005), echter lijkt deze correctiemethode niet optimaal voor het Nederlandse opleidingssysteem waarin opleidingsniveau een belangrijkere factor is dan het aantal jaren formele opleiding (Duits et al., 2014). In gezonde individuen werd gevonden dat prestaties op de MoCA beïnvloed worden door zowel opleidingsniveau als de geschatte premorbide intelligentie (Hoofdstuk 2). Daarop wordt in Hoofdstuk 3 een meer nauwkeurige correctiemethode voor opleidingsniveau geïntroduceerd, waarin één extra punt wordt toegekend aan individuen met een gemiddeld opleidingsniveau en twee punten aan individuen met een laag opleidingsniveau. Dit geeft een meer robuuste oplossing voor het overkomen van het effect van opleidingsniveau. Het gevonden effect van intelligentie op de MoCA was verwacht gezien bekend is dat intelligentie over het algemeen hoog correleert met opleidingsniveau in jongvolwassenen en volwassenen van middelbare leeftijd (Lezak et al., 2012) en het effect van aantal jaren opleiding op de MoCA al eerder gevonden was (Nasreddine et al., 2005; Zheng et al., 2012; Sugarman et al., 2014; Yancar Demir et al., 2015; Apolinario et al., 2018).

*Invloed van gebruiker gerelateerde eigenschappen*

De invloed(en) van verschillende aan gebruik gerelateerde eigenschappen, zoals het gebruikte middel, abstinentieduur, aantal jaren regelmatig gebruik, polygebruik, ernst van de verslaving en psychologische klachten zoals depressieve symptomen, angst en stress, werden ook onderzocht. Het gebruikte middel en abstinentieduur waren geen significante voorspellers voor prestatieverschillen op de MoCA (Hoofdstuk 3). Er dient echter opgemerkt te worden dat het effect van leeftijd op de MoCA significant was voor patiënten met een alcohol– of cannabisverslaving, maar niet voor de andere verslavende middelen. Er werd geen relatie gevonden tussen prestaties op de MoCA en de andere onderzochte eigenschappen: aantal jaren regelmatig gebruik, polygebruik, abstinentie, abstinentieduur, ernst van de verslaving en psychologische klachten (depressieve symptomen, angst of stress). Daarnaast werd in een groep patiënten met een GHB verslaving ook geen relatie gevonden tussen de MoCA–TS en ernst van het GHB gebruik (Hoofdstuk 6). Dat er geen relatie is gevonden tussen de MoCA–TS en psychologische klachten komt overeen met recente bevindingen in een groep polygebruikers waarin de MoCA–TS niet gerelateerd kon worden aan resultaten op een (psychiatrische) symptomenlijst (Hagen et al., 2019). Wat betreft abstinentie en abstinentieduur, beargumenteerde Walvoort et al. (2013) dat een minimale periode van zes weken abstinentie aanbevolen wordt voordat de belemmerende effecten van alcohol in het brein geminimaliseerd zijn en een NPO valide afgenomen kan worden. Echter is de MoCA een cognitieve screener die mogelijk minder gevoelig is voor de (sub)acute effecten van verslavende middelen dan een NPO. Daarnaast bestond de huidige groep niet enkel uit alcoholgebruikers.

***Prevalentie en verloop van neurocognitieve stoornissen in de verslavingszorg***

Nu enkele belangrijke psychometrische eigenschappen van de MoCA en de invloed(en) van verschillende (demografische/gebruiker gerelateerde) eigenschappen op de MoCA bekend zijn, is de volgende stap om de prevalentie en het verloop van cognitieve beperkingen in de verslavingszorg te onderzoeken.

*Prevalentie van neurocognitieve stoornissen*

Eerder onderzoek gaf een geschatte prevalentie van cognitieve stoornissen bij patiënten met een verslaving tussen 30% – 80% (Copersino et al., 2009). In het huidige onderzoek werd een prevalentie van NCS van 31% gevonden binnen de verslavingszorg. Dit grenst aan de bodem van het geschatte bereik. Verschillen in prevalentie tussen middelen waren niet zo uitgesproken als verwacht (alcohol = 34%; cannabis = 21%; stimulantia = 27%; opioïden = 38%). Dit zou echter beïnvloed kunnen zijn door het hoge percentage polygebruikers in de groep. In Hoofdstuk 6 werd een hogere prevalentie van cognitieve stoornissen gevonden, namelijk van 56%, in patiënten die vanwege hun GHB afhankelijkheid verwezen werden naar een detoxificatieafdeling. Dit is een groep waarin polygebruik ook niet ongebruikelijk is (Dijkstra et al., 2017).

*Verloop van cognitieve stoornissen gedurende behandeling*

Door de toereikende test–hertestbetrouwbaarheid en de beschikbaarheid van parallelle versies kan de MoCA gebruikt worden om het verloop van cognitieve prestaties over tijd te volgen bij patiënten met een verslaving. Dit was onderzocht in Hoofdstuk 5, in een groep van 524 patiënten met een alcoholverslaving die opgenomen waren in het Topklinisch Centrum voor Korsakov en Alcoholgerelateerde Cognitieve Stoornissen, en in Hoofdstuk 6 in een groep van 103 patiënten die in behandeling kwamen voor detoxificatie van GHB. In Hoofdstuk 5 werden significante verschillen gevonden in cognitieve prestaties tussen drie groepen patiënten met alcoholverslaving. Patiënten met Korsakov presteerden het laagst, gevolgd door patiënten met Cognitieve Stoornissen en die met enkel een alcoholverslaving, respectievelijk. Cognitieve prestaties verbeterden in alle drie de groepen tussen intake en de zesde week van opname, met een verdere verbetering tot aan het klinisch ontslag. Dit betekent dat alle patiënten met alcoholverslaving kunnen profiteren van langdurige klinische behandeling. In Hoofdstuk 6 werd eveneens een verbetering van cognitieve prestaties op de MoCA gevonden in patiënten met een GHB–verslaving, wanneer ze gemeten werden voor en na de detoxificatie. Kijkend naar de MoCA–DS, werd gevonden dat patiënten met Korsakov niet veranderden op het domein geheugen, terwijl patiënten met Cognitieve Stoornissen over alle drie de metingen verbeterden op dit domein. Bij patiënten met GHB–verslaving waren het prestaties op de domeinen geheugen en aandacht die indicatief leken voor een groter risico op terugval.

Naast cognitieve prestaties werd in Hoofdstuk 5 ook het alledaags cognitief functioneren gemeten middels zelfrapportage door de patiënt en klinische observaties door de eerst verantwoordelijke verpleegkundige (EVV). Patiënten beoordeelden hun cognitief functioneren hoger dan de EVV en de patiëntmetingen verschilden niet tussen de groepen. De EVV–metingen lieten daarentegen wel significante verschillen zien tussen de groepen. Deze bevinding is in overeenstemming met de literatuur waarin patiënten niet altijd subjectieve klachten rapporteren door een verminderd inzicht in hun eigen cognitieve tekorten (Walvoort et al., 2016). In tegenstelling tot bovenstaande, rapporteerden juist de patiënten een significante verbetering in het alledaags cognitief functioneren gedurende de behandeling, waar dit in de EVV–metingen niet gevonden werd. Een mogelijke factor hierin kan zijn dat de patiënten waarschijnlijk in een betere emotionele staat verkeerden toen ze de laatste meting invulden, gezien ze op dat moment abstinent waren en (bijna) met klinisch ontslag gingen. De veranderingen die gevonden zijn in cognitieve prestaties op de MoCA waren gerelateerd aan de veranderingen in het alledaags cognitief functioneren, ware het dat de effectgroottes laag tot matig bleven. Dit steunt de literatuur dat cognitieve prestaties op objectieve maten niet voorspellend zijn voor cognitieve beperkingen, in de afwezigheid van subjectieve ervaringen van alledaagse cognitieve problemen (Horner et al., 1999).

***Sterktes en beperkingen***

Elk deelonderzoek heft zijn eigen sterktes en beperkingen, die uitgebreid beschreven zijn aan het einde van elk hoofdstuk. Er zijn ook enkele algemene opmerkingen die gemaakt dienen te worden, wanneer het hele project wordt bekeken. Dit onderzoek vond zijn oorsprong in de klinische praktijk, waar enkele zeer gewaardeerde collega's hun handen en wijsheden hebben samengebracht en een plan formuleerden om een brug te slaan. Deze samenwerking tussen meerdere verslavingszorginstellingen resulteerde in een zogenaamd multicenter–project van waaruit grote groepen patiënten konden worden geïncludeerd. Er is een belangrijk punt dat gemaakt moet worden wanneer we onze bevindingen interpreteren, met name de bevindingen gerelateerd aan de prevalentie van NCS. Zoals reeds in de introductie beschreven is, is het aantal patiënten dat zich in de verslavingszorg aanmeld voor behandeling naar alle waarschijnlijkheid slechts het puntje van de 'gebruikers'–ijsberg. Epidemiologisch is het onmogelijk te weten wat middelengebruikers die zich niet aanmelden voor enige vorm van behandeling gebruiken en of zij eventuele cognitieve beperkingen hebben of niet. Daarnaast werden er respectievelijk een lage tot matige voorspellende (*predictive*) en gelijktijdige (*concurrent*) validiteit van de MoCA gevonden, wat maakt dat de daadwerkelijke prevalentie van NCS zeer anders kan zijn dan in dit onderzoek gevonden. Doordat we onze groepen patiënten echter zeer goed hebben kunnen omschrijven in termen van welke middelen ze gebruiken, hoeveel en voor hoe lang, zijn ze representatief voor de populatie van middelengebruikers/–misbruikers. Dit maakt de resultaten hoogst generaliseerbaar. Het blijft altijd de vraag (zoals ook hierboven beschreven over cognitieve klachten), in welke mate het middelengebruik objectief gemeten kan worden door zelfrapportage. We hebben dit zo goed mogelijk proberen te ondervangen door gebruik te maken van een wetenschappelijk aangetoond en gevalideerd interview dat de relevante patiënteigenschappen in de verslavingszorg in kaart brengt: de MATE (Schippers et al., 2011).

***Overwegingen voor de klinische praktijk***

Nu, aan het einde van dit project, is de beschikbaarheid van de MoCA gestegen naar meer dan honderd talen in zestig landen. De screener is constant in ontwikkeling gebleven en er zijn nu ook verschillende vormen beschikbaar. Denk hierbij aan een telefonische screening of een vorm voor blinden, maar ook de app–versie is beschikbaar. Het onderzoek waarin de MoCA gebruikt wordt groeit met gepaste snelheid. Aan het begin van dit promotietraject waren er slechts enkele studies die de bruikbaarheid en toepasbaarheid van de MoCA in de verslavingszorg hadden onderzocht. Het aantal gepubliceerde artikelen over dit onderwerp is inmiddels gestaag gegroeid en groeit sindsdien nog steeds.

De MoCA voldoet niet geheel aan de criteria waaraan een ideale cognitieve screener zou moeten voldoen. Zo zijn prestaties niet onafhankelijk van leeftijd, opleidingsniveau, premorbide geschatte intelligentie en type middel. Daarom zouden er meer uitgebreide, gelaagde of op regressie gebaseerde normen ontwikkeld moeten worden, die corrigeren voor leeftijd, opleiding en intelligentie. Desalniettemin dient nogmaals benadrukt te worden dat de MoCA een cognitieve screener is en geen diagnostische maat. Dus zelfs als een screener een uitstekende sensitiviteit en specificiteit heeft, blijft een NPO de goudstandaard voor diagnostische overwegingen, zoals ook specificaties van specifieke cognitieve profielen.

In de loop van dit project vonden we dat de bewustwording van het bestaan van cognitieve stoornissen (NCS) in de verslavingszorg gegroeid is en nog steeds groeit. Bekijk hiervoor bijvoorbeeld ook het recent uitgekomen alomvattende handboek van Verdejo–García (Cognition and addiction: a researcher's guide from mechanisms towards interventions [Cognitie en verslaving: een gids voor onderzoekers van mechanismen tot interventies]; 2020). Wanneer de MoCA gebruikt wordt om te screenen op cognitieve beperkingen in de verslavingszorg, is het belangrijk dat leeftijd, opleidingsniveau en het type middel in acht worden genomen bij het interpreteren van de resultaten. De MoCA–TS en –MIS zijn de meest betrouwbare en valide scores, waar de MoCA–DS veel minder betrouwbaar en valide zijn. Mocht iemand toch uitspraken willen doen over specifieke domeinen, dan lijken lage scores op het domein geheugen voorspellend voor de aanwezigheid van NCS. Als deze scores over tijd niet verbeteren is dit een indicatie voor ernstige NCS. De MoCA kan daarnaast gebruikt worden om cognitieve prestaties gedurende het behandelverloop te monitoren. Met name bij patiënten die klinisch opgenomen zijn, zien we niet alleen in de eerste zes weken een verbetering van cognitieve prestaties, maar ook verder gedurende de behandeling.

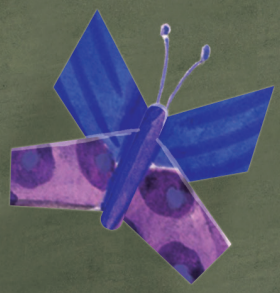
Men moet zich altijd bewust zijn van de sensitiviteit en specificiteit op verschillende afkapwaarden. Als men een patiënt met cognitieve beperkingen niet wil missen bij de screening, denk er dan over om de afkapwaarde vooraf aan de meting te verhogen. Een lagere vooraf bepaalde afkapwaarde verlaagt daarentegen de kans op het foutief indiceren van beperkingen waar deze er niet zijn. Het gebrek aan ziekte–inzicht in het eigen cognitieve functioneren, dat met dit onderzoek bevestigd werd, laat daarbij het belang zien van screenen op een vroeg moment in de behandeling zodat de gevonden resultaten kunnen helpen bij het maken van gepaste beslissingen.

***Tot slot…***

De MoCA is niet de 'ideale screener' waar we naar zochten, maar op dit moment is het wel de beste keuze. Als een ideaal screeningsinstrument al bestaat, hoe zou dit er dan uit moeten zien? Zijn er andere veelbelovende kandidaten op de markt? Of is de nieuwe en verbeterde MoCA versie 8 al het instrument dat de tekortkomingen die in dit proefschrift omschreven zijn kan overkomen? Tot nu toe heeft de MoCA zeker enkele duidelijke voordelen en is het de beste optie die er is. De MoCA heeft zijn weg naar de Nederlandse verslavingszorginstellingen al gevonden en de bewustwording van de cognitieve gevolgen van langdurig middelengebruik is de afgelopen jaren gestegen. Dit zijn reeds zeer belangrijke stappen op onze weg naar het verder reduceren van de invloed die verslaving op onze maatschappij heeft en het plannen van behandeling op maat.

Zoals ik al zei, mijn slotbetoog. Ik begon mijn dankwoord bij familie, Koos, en wil het ook eindigen bij familie: mijn ouders, zussen, en schoonfamilie. Ik begin bij de laatste, mijn schoonfamilie: Hennie, Theo en Bertha, bedankt dat jullie mij in jullie families hebben opgenomen, een warm thuis hebben gegeven en met open armen ontvangen hebben. Bedankt voor alle hulp die jullie de afgelopen jaren geboden hebben en nog altijd bieden. Ook als wij niet eens in de gaten hebben dat het nodig is.

Lieve Lieke, mijn 'nieuwste zus', bedankt dat ik jou familie mag noemen. Je bent een super vriendin voor mij en peettante voor Jeste. Ook jij staat altijd voor ons klaar, en het wordt tijd dat ik er ook meer voor jou kan zijn.



# Appendix

## Curriculum vitae

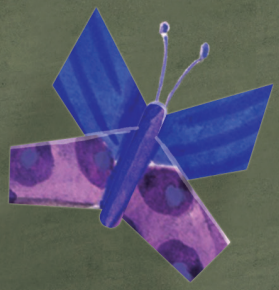
# Curriculum vitae

Carolien Zeetsen–Bruijnen werd geboren op 27 juni 1985 te Maasbree. In 2003 behaalde zij haar havo diploma aan het Bouwens van der Boijecollege te Panningen, waarna zij in 2004 haar propedeuse Toegepaste Psychologie aan de Fontys Hogeschool te Eindhoven in ontvangst nam. Met deze propedeuse werd zij in 2004 toegelaten tot de opleiding Psychologie aan de Universiteit Maastricht, alwaar zij in 2009 haar Bachelor Biologische Psychologie behaalde. In 2011 volgde de Master Neuropsychologie, eveneens aan de Universiteit Maastricht. Hiervoor liep zij in 2010 een wetenschappelijke stage op de afdeling Psychiatrie van Stellenbosch University in Kaapstad, Zuid–Afrika. Haar klinische stage liep ze in 2011 bij het Topklinisch Centrum voor Korsakov en Alcohol–gerelateerde Cognitieve Stoornissen van Vincent van Gogh. In januari 2012 begon ze haar wetenschappelijk onderzoek alhier, onder de vleugel van het Nijmegen Institute for Scientist–Practitioners in Addiction (NISPA). In ditzelfde jaar startte ze binnen het Korsakov Centrum als psychodiagnostisch medewerker en later als psycholoog. Vanaf dit moment heeft ze wetenschappelijk onderzoek gecombineerd met werken in de klinische praktijk. In 2014 werd het onderzoek tot een promotietraject omgedoopt. In april 2019 is ze kortdurend als psycholoog gaan werken bij AltraCura, een behandelsetting voor volwassenen met het vermoeden van ASS en/of ADHD. Na het faillissement van dit bedrijf in november datzelfde jaar, is ze in januari 2020 begonnen als psycholoog bij de Mutsaersstichting, een instelling voor kind– en jeugdzorg, alwaar zij momenteel werkzaam is. In de tussentijd heeft zij naast deze werkzaamheden in eigen tijd dit proefschrift afgerond om op 4 december haar PhD te behalen.

Linda, Jacqueline en Marjo, mijn grote zussen. We zijn samen opgegroeid op het platteland van Maasbree, waar we alle ruimte hadden en ook kregen, om te kunnen spelen, ontwikkelen, puberen en opgroeien tot de vrouwen en moeders die we nu zijn. Doordat we in leeftijd verschillen en soms in verschillende werelden leken te leven zijn we elkaar met momenten misschien wat uit het oog verloren, maar we vinden elkaar altijd weer terug. Wat ben ik trots dat ik jullie kleine zusje ben.

Cris, Roy en Antoine, mijn ('schone')broers. Door de jaren heen zijn jullie in mijn leven gekomen. Wellicht dat ik in het begin voor jullie dat 'vervelende kleine zusje' was, dat altijd overal bij wilde zijn. Maar ook wij zijn door de jaren opgegroeid tot echte familie. Ik ben blij dat mijn zussen jullie gevonden hebben, bedankt dat jullie er zijn.

Merlijn, Colin, Josh, Lennon, Joni en Iwan ik ben super trots dat ik mij jullie tante mag noemen. Vanaf het eerste uur heb ik door jullie alles in perspectief kunnen plaatsen, hoe klein jullie begonnen zijn en hoe groot jullie al worden. Bij jullie voel ik mij weer even kind.



# Appendix

## List of publications

# List of publications

***This dissertation***

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. (2019). The Montreal Cognitive Assessment (MoCA) as a cognitive screen in addiction health care: a validation study for clinical practice. Journal of Substance Use, 24(1), 47–54. https://doi.org/10.1080/14659891.2018.1497102

Bruijnen, C.J.W.H., Dijkstra, B.A.G., Walvoort, S.J.W., Markus, W., VanDerNagel, J.E.L., Kessels, R.P.C., & de Jong, C.A.J. (2019). Prevalence of cognitive impairment in patients with substance use disorder. Drug and Alcohol Review, 38(4), 435–442. https://doi.org/10.111/dar.12922

Bruijnen, C.J.W.H., Dijkstra, B.A.G., Walvoort, S.J.W., Budy, M.J.J., Beurmanjer, H., de Jong, C.A.J., & Kessels, R.P.C. (2020). Psychometric properties of the Montreal Cognitive Assessment (MoCA) in healthy participants aged 18–70. International Journal of Psychiatry in Clinical Practice, 24(3), 293–300. https://doi.org/10.1080/13651501.2020.1746348

Bruijnen, C.J.W.H., Walvoort, S.J.W., Dijkstra, B.A.G., de Jong, C.A.J., & Kessels, R.P.C. (ahead of press). The course of cognitive performance during inpatient treatment in patients with alcohol use disorder (AUD) with no, mild, or major neurocognitive disorders (NCD). Alcohol & Alcoholism.

***Other publications***

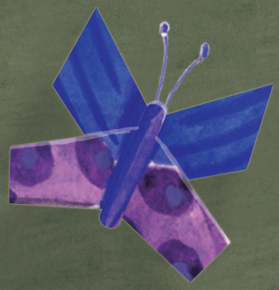
Bruijnen, C.J.W.H., Kessels, R.P.C., Dijkstra, B.A.G., Walvoort, S.J.W., Wester, A.J., & de Jong, C.A.J. (2016). Montreal Cognitive Assessment – Dutch (MoCA–D): een cognitieve screener in de Nederlandse reguliere verslavingszorg [Montreal Cognitive Assessment (MoCA): a cognitive screen in addiction health care] (NISPA, Ed.). Nijmegen.

Bruijnen, C.J.W.H., Young, S.Y., Marx, M., & Seedat, S. (2019). Social anxiety disorder and childhood trauma in the context of anxiety (behavioural inhibition), impulsivity (behavioural activation) and quality of life. South African Journal of Psychiatry, 25, 1–7. https://doi.org/10.4102/sajpsychiatry.v25i0.1189

***In preparation***

Beurmanjer, H., Bruijnen, C.J.W.H., Greeven, P.G.J., de Jong, C.A.J., Schellekens, A., & Dijkstra, B.A.G. Cognitive impairments in patients with GHB use disorder predict relapse in GHB use.

Mam en pap, Maria en Jos, jullie hebben me geleerd voor mezelf op te komen, door te gaan totdat ik bereikt heb wat ik wilde. Vandaag ben ik daar al een heel eind mee gekomen! Bedankt dat jullie mij altijd vertrouwd hebben, ook op die enkele momenten dat ik dit vertrouwen als puber schaadde. Jullie hebben allebei kei hard gewerkt om mij te kunnen geven wat ik nodig had. Ik kwam niks tekort, op geen enkel front. Door jullie ben ik geworden wie ik ben, ik ben trots op jullie!



# Appendix

## Research data management

# Research data management

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles (Wilkinson, M., Dumontier, M., Aalbersberg, I. et al., 2016, The FAIR Guiding Principles for scientific data management and stewardship. Scientific Data, 3, 160018. https://doi.org/10.1038/sdata.2016.18). The paragraphs below specify in detail how this was achieved.

### *Ethics*

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board of Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands approved the patient research, the research in healthy participants was approved by the Faculty of Social Sciences Ethics Committee of Radboud University, Nijmegen, the Netherlands (ECSW2017–2306–520).

### *Funding*

The research was supported by the Nijmegen Institute for Scientist–Practitioners in Addiction (NISPA) and Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands.

### *Findable, Accessible*

Anonymized data of all empirical chapters are available in the Donders Repository https://doi.org/10.34973/g9ag-w336. Informed consent was obtained on paper. The forms are archived at the Centre of Excellence for Korsakoff and Alcohol–Related Cognitive Disorders of Vincent Van Gogh Institute for Psychiatry, Venray The Netherlands. All response forms from the neuropsychological assessment are stored at the Centre of Excellence as well. Data will be stored for 10 years (from 01–12–2020) and may then be destroyed.

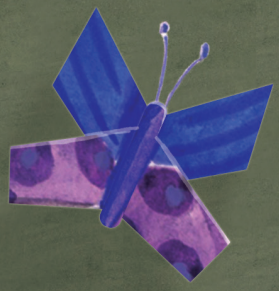
### *Interoperable, Reusable*

The raw data are stored in SPSS format. A description of the experimental setup can be found in published articles.

### *Privacy*

The privacy of the participants in this thesis has been warranted using individual subject codes. The keys are also stored at the archives of the Centre of Excellence and are only accessible to members of the project who needed access to it because of their role within the project. The keys are stored separately from the research data.

Tot slot mijn allerliefste ‘goudlokje’, Jeste. Je bent mijn alles, mijn wereld. Elke keer als ik naar je kijk, zie ik een ander meisje, je groeit en leert zo ontzettend snel dat ik je soms niet bij kan houden. Jij zorgt ervoor dat ik met beide voeten aan de grond blijf, dat ik blijf genieten van de kleine dingen. Ik geniet ontzettend van je knuffels en kusjes (en dat zijn er veel!) en nog meer als je lekker op de bank tegen me aan kruipt. Je bent mijn anker. Ik hou van jou tot de ruimte...



# Appendix

## Donders series

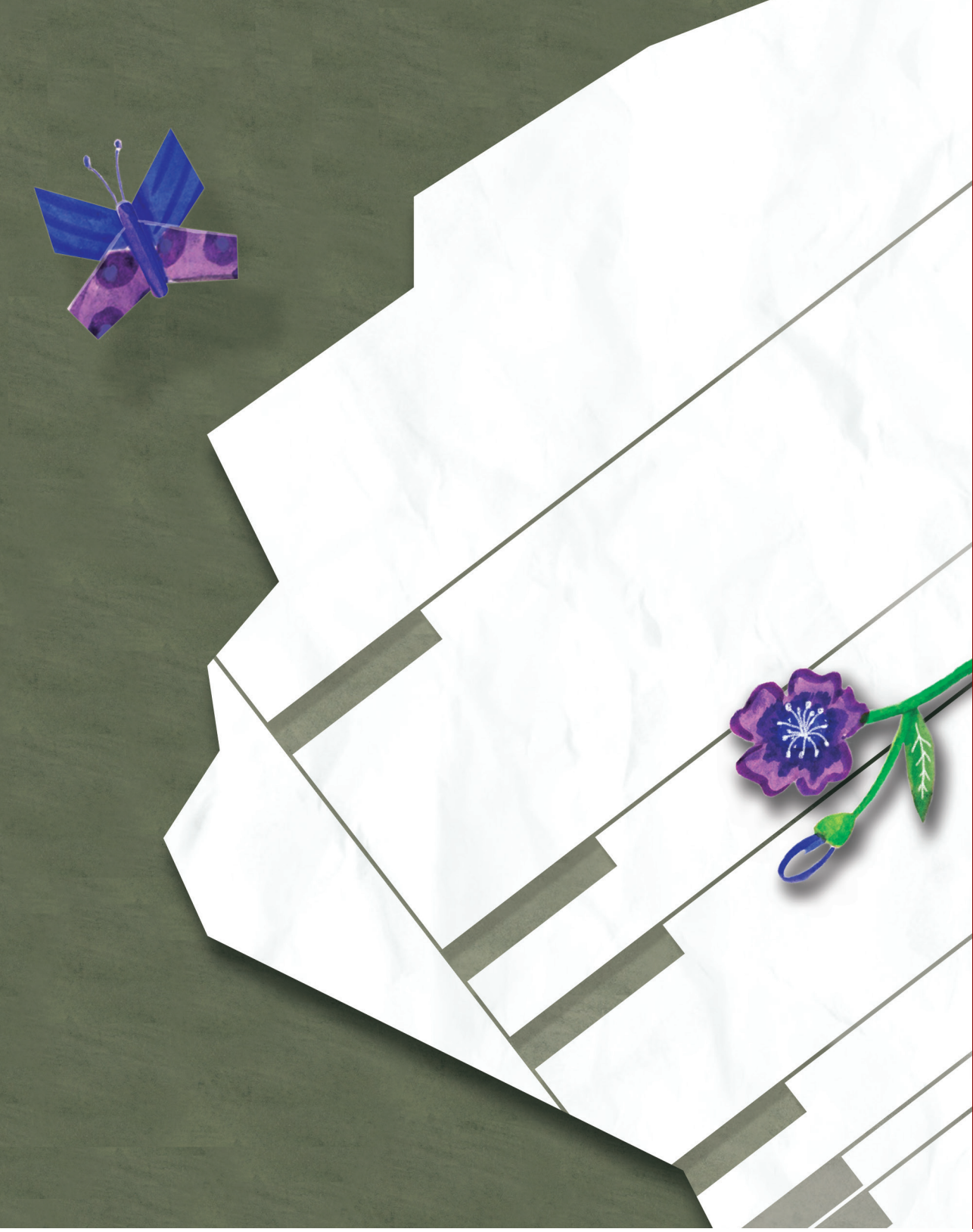
# Donders graduate school for cognitive neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioural science, medicine and related disciplines. Selective admission and assessment centres guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, North–eastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high–quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defences please visit: http://www.ru.nl/donders/graduate-school/phd/



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