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2022

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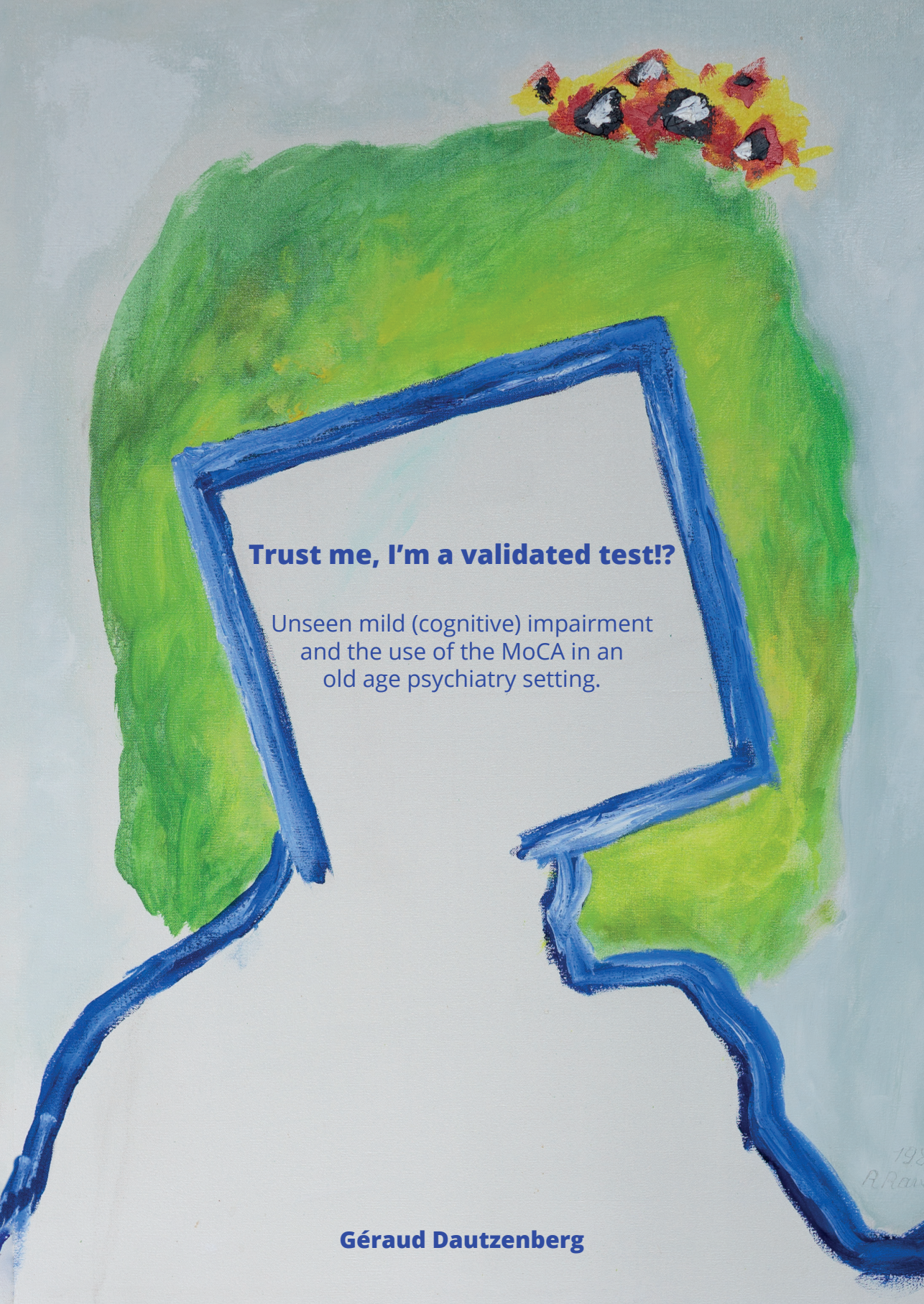

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Unseen mild (cognitive) impairment
and the use of the MoCA in an
old age psychiatry setting.

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Colofon

The research described in this dissertation was conducted at and financially supported by the department of old age psychiatry of Altrecht, Utrecht the Netherlands.

The dissertation was prepared at the department of psychiatry, Amsterdam UMC, VU university Amsterdam within the Amsterdam Public Health research institute.

Printing of this dissertation has been accomplished with gratefully acknowledged financial support, provided by de Vrije Universiteit Amsterdam and Alzheimer Nederland (Amersfoort).

ISBN: 978-94-6458-708-1

Cover: Roger Raveel - Nog een beetje mens. www.rogerraveelmuseum.be
Cover-photo and -design: Jantine Messing / Coen van der Bijll
Dissertation lay-out and design: Coen van de Bijll (Ridderprint/Publiss)
Printing: Ridderprint, www.ridderprint.nl

VRIJE UNIVERSITEIT

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 13 december 2022 om 11.45 uur
in een bijeenkomst van de universiteit,
De Boelelaan 1105

door

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geboren te Heerlen

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CHAPTER

General introduction

1

1. GENERAL INTRODUCTION

1.1 Why

Why this study?

Why for me?

1.2 When

1.3 Where

1.4 Who

1.5 What

What test do we use?

MoCA, CANE

What do we mean (definitions)?

Need, MCI, dementia, cognitive domains, depression, bipolar disorder, schizophrenia, doctors delay, patients delay

1.6 How

Aim and outline of the dissertation

1.1 Why

1.1.1 Why this study?

In old age psychiatry, one can encounter a broad variety of referrals, at least in the Netherlands. Predominantly patients with affective disorders, anxiety disorders, psychotic disorders, and cognitive disorders are referred. Very few of the symptoms of these disorders are specific to only one psychiatric disorder and even 'typical' complaints can mimic, different aetiologies (American Psychiatric Association, 2013). This increases with age, as patients tend to have complaints in more than one specific domain, and often the complaints cannot be attributed to just one cause (Bierman *et al.*, 2007; Schouws *et al.*, 2012; Baune and Renger, 2014; Bora and Pantelis, 2015). Giving up hobbies is often wrongly attributed to being too old or being socially isolated, but can (also) be due to an affective disorder, negative symptoms of (late-onset) schizophrenia, side effects of medication (ranging from a tremor to cognitive impairment), or a developing neurodegenerative disorder expressing itself in apathy. Therefore, in old age psychiatry, complaints can result from more than one of the 'classical psychiatric diseases', as encountered in textbooks (Ferri *et al.*, 2005). Often, age, frailty, social isolation, mobility, polypharmacy, comorbidity, and neurodegenerative diseases contribute to the overall picture owing to its population. This is most prominent in cases of cognitive impairment. A simple but daily example is a patient of age that has limited mobility, is depressed, uses psychotropic medication, and experiences (subjective) cognitive decline, and (therefore) quits his bridge club, for example, because of the shame of not being able to play at their former level. Giving up this activity can find its origin in either of these causes. Of course, none of these factors could be significant enough to cause mild cognitive impairment (MCI) by itself, but when combined, they would be. Furthermore, it can of course be neither of the above but an emerging neurodegenerative process or social deprivation causing depressive symptoms with subjective cognitive impairment causing fear of embarrassing oneself. Disentangling the possible aetiologies seems simple in theory, but the clinical reality is harsh. Simply stopping the antidepressant that seemed effective, to see if it was indeed the presumed side effects that caused cognitive impairment, is easier said than done. Alternatively, could it be that depression was only partly in remission, and cognitive impairment is a remaining symptom? Waiting for depression to subside does not take into account that cognitive deficits can linger even after the clinical depression has subsided (Ahern and Semkovska, 2017; Riddle *et al.*, 2017; Semkovska *et al.*, 2019). Was there already a neurodegenerative process developing in the background as 15% of 70 years and older and increasing to over 30% of 85 years and older have dementia, and

even more so will have (mild) cognitive impairment (Volksgezondheidenzorg.info, 2019; '2020 Alzheimer's disease facts and figures', 2020)? Alternatively, were fear, shame, and loneliness key? Moreover, could disproving the subjective cognitive impairment through an objective test and organising transportation to the bridge club do the trick? For these questions to be answered with more certainty, one needs to judge cognitive complaints. Unfortunately, subjective cognitive complaints are poorly correlated with objective cognitive deficit (Pendlebury *et al.*, 2015). This also accounts for next of kin reports and even more so for retrospective recall (Ryu *et al.*, 2020). In addition, for being able to define a state, one must be able to compare it. This is often done in comparison to normative data, that is, the data of others resembling the patient in age and education. However, it would be even better to know the course and, therefore, be able to compare the patient with herself over time. In the above example, the issue would be simplified if there were a baseline at our disposal: was there already cognitive impairment, and if so, did the cognitive impairment change over time? During the depression, or was there a time correlation with recovery or after starting medication? There are many reasons why one wishes for some solid ground when assessing cognitive function in old age psychiatry.

But the above all comes down to:
Testing is objectifying. However, validated comprehensive tests that can help distinguish between the different aetiologies are not widely available in the short term. Therefore, not only is a short, rapid implementable test needed, but it also needs to be validated to interpret the results. Whether one needs to determine to exclude cognitive impairment or notice cognitive impairment at an earlier stage.

1.1.2 Why for Me?

The Minimal Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975) — I presume that most medical doctors are familiar with it — is a cognitive test to objectify cognitive impairment or screen for dementia or other severe cognitive impairments. It is a practical bedside test (a short questionnaire using only paper and pencil). Even though it was introduced in 1975, it still was at the beginning of my research, or even still is a sort of standard of short cognitive screeners when cognitive impairment is suspected (alzheimer-nederland.nl). However, its major shortcoming is a ceiling effect, meaning that less severe impairments would not be noticed by the MMSE or higher educated persons could pass the test even if they have impairments (Mitchell, 2017; Pinto *et al.*, 2019). Therefore, at the beginning of my career as an old age psychiatrist, I was trying to select a cognitive test that would better fit my daily clinical use, including house visits, in correctly

identifying mild cognitive impairments. Therefore, they still need to be easily applicable, accessible, and affordable. During a home visit consultation in 2008 regarding a patient with lithium intoxication, I also added routine cognitive screening. In this case a 'new' cognitive screener: the Montreal Cognitive Assessment (MoCA) was used (Nasreddine *et al.*, 2005). This was more to gain experience with new cognitive screening instruments and which one to use from now on as I did not expected major abnormalities. This is partly because I had gone through an extensive complaint anamnesis with the patient, which was focused on her lithium use and its side effects. As it turned out, I overestimated that significant cognitive abnormalities would have been 'à vue' for me as an old age psychiatrist to notice. You are holding the result of that test in your hands in the form of this dissertation. Of course, this example could not be the only patient with unknown cognitive impairment, intervening with the treatment. In her case, there was a (lithium) intoxication as she forgot that she had already taken her lithium and therefore mostly likely doubled her dose by mistake. Not considering this would be a mistake and prone to more foreseeable mistakes.

Being confronted with my own shortcomings, even though the reason for the consultation had a different origin, I had fallen into a classical nicely put 'doctors delay' trap. I realised that the needs patients mention do not necessarily correspond with the needs the doctor hears, sees, or thinks should be met (by him or her). Furthermore, even those needs that the patients want or need to be met are not necessarily the ones they mention to be met, that is, 'patients delay'. This can have multiple reasons, ranging from being unaware of their need to denial of their need, fear of being stigmatised, or thinking a doctor cannot help them with their particular needs.

These "delays" result in the following question:

When should we screen?

1.2 When

The discussion above illustrates well the dilemma that doctors face on a daily basis. To what extent do they have to look for something that is not (yet) a problem, that is not seen or experienced as such (by the doctor or by the patient), or is not recognised as such. Or, when it is a problem but not (yet expressed as) a complaint? Does the patient always have the right to downplay or even ignore the problem? The COVID-19 pandemic is illustrative in that there is no obvious answer on second sight. This dilemma occurs also often with cognitive impairment, as many patients don't want to have an elaborate

cognitive assessment as they find it a hassle, too demanding or deem it 'much ado about nothing'. Sometimes, they do not want to be confronted or diagnosed with cognitive impairment. This can be due to multiple reasons, ranging from fear of losing their driving licence to denial of the impairment. Another situation is that the patient is not aware of their cognitive decline and only afterwards realises the consequences of a diagnosis. However, this right to ignore can result in dangerous situations, such as cooking at home resulting in the cooking stove not being turned off afterwards. Is this a problem for the doctor to resolve? Is it only his or her concern or responsibility if a complaint or problem leads to a medical problem? Doctors primarily want to help. However, the Hippocratic Oath states "First, do no harm" (Latin: *Primum non nocere*). To what extent is helping the individual lead to harming others, for example, by screening all patients to find a few cases and using scarce resources? Or 'helping', that is, not diagnosing a patient on their request so they won't be stigmatised. Therefore, avoiding a ban on driving but perhaps becoming a risk for all traffic participants?

This is plenty of material to consider and debate. On many levels, medical, ethical, philosophical, political, and so on, all the way up to the (patients) kitchen table. Therefore, this debate is far from over. The debate varies across subjects and settings, ranging from clinical themes (e.g. diseases) to social (e.g. loneliness) or financial (e.g. healthy food) issues. One must bear in mind that the outcome of the debate will be different for screening individual patients than for screening the general population. In clinical practice, doctors often use guidelines that give them something to hold on to. One of these 'guidelines' is a list of requirements, or rather criteria, for screening populations, which was drawn up in 1968 on behalf of the World Health Organization WHO (Wilson and Jungner, 1968). They were still relevant up until today (Sturdy *et al.*, 2020).

These criteria are summarized by the RIVM (Dutch national health institute) as follows:

'*….a screening that falls under the national population screening program must be of benefit to participants, voluntary, and scientifically based. To determine whether a screening is justified, international criteria were drawn up by Wilson and Jungner in 1968*'.

Table 1. Criteria of Wilson and Jungner (1968)

1 The disease to be detected must be a major health problem.
2 There must be a generally accepted method of treatment for the disease.
3 There must be adequate facilities for diagnosis and treatment.
4 There must be a recognizable latent or early symptomatic stage of the disease.
5 A reliable detection method must exist.
6 The detection method must be acceptable to the public.
7 The natural course of the disease to be detected must be known.
8 There must be agreement as to who should be treated.
9 The cost of detection, diagnosis and treatment must be in an acceptable proportion to the cost of health care as a whole.
10 The process of detection must be a continuous process and not a one-time project.

In 2008, a list of additional criteria was drawn up by the World Health Organization (WHO).

Although the abovementioned criteria are intended for large-scale screenings, such as national population studies, they can also be used as guidance for small-scale screenings. Think of local initiatives or specific patient groups. It becomes less clear when screening is used on an individual basis for complaints that would otherwise be overlooked. Or when it concerns using the screener as a severity scale. It is doubtful whether this is still a screening in itself, or whether it is more about using a screener to follow the course of a disease for an individual situation. Other ethical criteria, which are usually enshrined in health laws, will come into effect. However, what if the "on indication" is applied to all (referred) patients? Therefore, we will consider the WHO criteria as a starting point, but not as a rule.

Several criteria enumerated by the WHO are touched upon in this dissertation, whereas many are not answered for various reasons. The most important reason is that the criteria themselves are not the subject of our study, but we use them as guidelines.

As the above personal clinical experience illustrates, it is easy to overlook (or ignore) other matters that are at hand, such as social isolation or cognitive impairment (the underlying cause of a problem?), when your attention is focused on something else (the main complaint). In particular, when efficiency is expected due to time constraints and costs, to minimise waiting lists. Screening can never be a substitute for a thorough diagnostic workup. However, can screening not be a helping hand? If so, when should one consider screening?

In addition to the above criteria, when a screening is justified, there are also costs. These costs should not be limited to the financial sphere (Table 1, criteria 9). There are many

factors to be considered besides spending on resources, efficiency, and so on. Screening takes its toll in many areas, but the benefits of screening should always outweigh its disadvantages. These negative factors also depend on where, that is, in which setting or for which population, the screening takes place. Haphazardly screening the general population costs more than it will yield.

Therefore, it should not only be considered when (or for what) to screen but also *where* to screen.

1.3 Where

Particularly in geriatric psychiatry, the symptoms of several aetiological entities resemble or even overlap each other. Not only is it difficult to distinguish the aetiologies one from the other, but sometimes they coexist and contribute to the same complaint (to some extent). One particular entity is always present in an old age psychiatric practice: old age. Where living its life has left its mark on many patients. However, where do these traces of old age turn into 'no longer appropriate for age, education, and social context'? Alternatively, they have a (negative) impact on the quality of life, even if they are (still partly) appropriate for their age or social context. When is an intervention justified if they negatively affect 'wellbeing'? How much of it must deteriorate before it can be called a disease? Who is to judge if someone's 'wellbeing' needs to be improved? If so, which domains should be prioritised? Is that for the doctor to decide, the next of kin representing society, or is the decision of the main character, that is, the patient? This accounts for different domains, such as social, psychological, and physical, but this is especially true for cognitive impairment. These questions or dilemmas can only be solved if one also has insight into the complaints and how much they play a role: *the quantitative part*.

In old age psychiatry, these factors play a significant role as they tend to add up known as 'frailty', more than in other disciplines where they may seem to be in the background or have no influence at all. These factors not only include age-appropriate problems, but also the field of geriatric psychiatry. Geronto-psychiatry and psychogeriatrics have always been the core of old age psychiatry. Where the psychiatrist for (younger) adults can focus on the complaints of her patient without worrying about age-related complications or comorbidities, in old age psychiatry this will always have to be considered. However, the extent to which age alone plays a role in the clinical picture of elderly patients, and to what extent (complications of) age cause a different form of the disease or even another disease? Is it more of the same problem (compared to a younger patient) or is

it a different problem? There are indications that in older patients with, for example, a bipolar or depressive disorder, a different manifestation or even a type of this disorder may be at hand (Sajatovic *et al.*, 2015; Aizenstein *et al.*, 2016). In particular, if the disorder arises only for the first time at a later age (i.e. late onset or very late onset), the expected neurodegenerative disorders that occur with advancing age can also play a role, in both numbers (prevalence) and severity. One has to bear in mind that the prevalence of dementia is already up to 10% from 65 years of age and above (Volksgezondheidenzorg.info, 2019; '2020 Alzheimer's disease facts and figures', 2020). Our colleagues, who also deal with neurodegenerative disorders (neurologists, clinical geriatricians), normally do not often have other psychiatric diseases among their referrals that cause cognitive impairment. Of course, they still need to be aware of them. In The Netherlands, referrals to old age psychiatry consist of a mix of neurodegenerative and other psychiatric disorders, such as depression, bipolar disorders, schizophrenia, and severe anxiety disorders, all of which can be accompanied by poor (long-term) cognitive functioning (Bierman *et al.*, 2005; Schouws *et al.*, 2012; Baune and Renger, 2014; Bora and Pantelis, 2015; Ahern and Semkovska, 2017; Riddle *et al.*, 2017; Semkovska *et al.*, 2019; Van Rheenen *et al.*, 2019). In contrast, dementia can frequently be accompanied by depression, hallucinations, delusions, and anxiety (Lyketsos *et al.*, 2002; Di Iulio *et al.*, 2010). Both neurodegenerative and psychiatric diseases often present themselves with symptoms normally attributed to the other entity before their 'classic features' appear (Lyketsos *et al.*, 2002; Reichenberg, 2010; Eikelboom *et al.*, 2021). We will later elaborate on the overlapping presentation in the definition paragraph. However, for these questions to be answered, one needs insight into the causal entities' or aetiology behind the complaint: *the qualitative part*.

In addition to the 'quantitative' and 'qualitative' reasons for knowing the cognitive function of a patient in old age psychiatry, there are other reasons for cognitive screening. As mentioned above, the prevalence of MCI and dementia above 60 years of age is high in the general population, and this will be even higher in an older psychiatric setting. The population of older people is increasing owing to demographic factors. This eventually results in more older patients having psychiatric problems. This, in turn, will increase the number of psychiatric patients with cognitive complaints in addition to the expected increase in patients with neurodegenerative disorders. This will lead to an increase in referrals to older psychiatric clinics for patients with cognitive impairment. Together with more awareness due to public campaigns on cognitive impairment, there is also a trend of being assessed earlier in the process with fewer complaints (Grimmer *et al.*, 2015). Some of them had only subjective complaints without being able to objectify these complaints. Even

so, most patients with dementia will stay undiagnosed, 50% in developed countries and up to 90% in poor countries (Alzheimer's disease International, 2016). A part of the public campaigns by advocacy groups or policymakers is to stimulate patients as well as healthcare professionals for more (early) diagnoses. This will result not only in more referrals but also in more referrals with less well-described cognitive impairments, and it will be harder to differentiate aetiologies (Mitchell, 2009). A detailed neurocognitive assessment, which is costly, time-consuming, and not widely available, is advised by advocate groups in the case of cognitive complaints. However, doing so for all patients with cognitive complaints will be an assault on available resources. The cognitive diagnostic tracks in memory clinics or old age psychiatry clinics are already being challenged and will be further challenged due to the increase in the older population (Alzheimer's Disease International, 2018). Moreover, many subjective or even objective (mild) cognitive complaints (up to 40%) will subside or decrease over time (Alexopoulos *et al.*, 2006). Selecting patients who are in need of this elaborate neurocognitive assessment would help reduce the burden on resources. We have to find patients who benefit from an elaborate neurocognitive assessment better, or in other words, triaging those who are in need of a specialised neurocognitive assessment and who are not (yet) in need of such assessment.

Unfortunately, this leads to more questions: '*who*' is in need and '*how*' do we find them?

1.4 Who

A way to achieve early detection and to find those in need of an elaborate assessment is through screening. Advocacy groups for dementia encourage this, but the debate on whether screening is a solution or wise is still debatable (Borson *et al.*, 2013; Davis *et al.*, 2015; Burn *et al.*, 2018). Many factors must be considered, such as spending resources and efficiency. One of the main issues is which population to screen, for what purpose, and what instrument to use (Janssen *et al.*, 2017). As screening for cognitive impairment in a general practitioner's office will result in different findings than at a memory clinic or in old age psychiatry, more people are likely to have cognitive impairment. Screening with a fast and cheap instrument will result in different findings than screening with a more time-consuming and multi-factor full assessment. The first example yields a high quantity with low quality, but the latter example, on the contrary, yields high quality and low quantity. Additionally, the purpose of screening should be considered. In a test, specificity and sensitivity always compete with precedence. Which one should prioritise depends on the purpose of the test. Screening for HIV can serve as an example of this. At the doctor's office, you want to establish a definite diagnosis. You do not want to

diagnose someone falsely. This translates into no 'false positives', that is, high specificity. However, at the blood bank, you want to rule out the disease with certainty. This, in turn, translates into no 'false negatives', you do not want to miss a case (high sensitivity).

In old age psychiatry, regarding cognitive complaints, we can organise the population by cognitive complaints, cognitive functioning, and whether they have psychiatric complaints or not. Creating groups using these three parameters results in: not suspected of cognitive impairment (but with psychiatric symptoms), suspected of but not objectified (with or without psychiatric symptoms), and objectified cognitive impairment (with or without psychiatric symptoms).

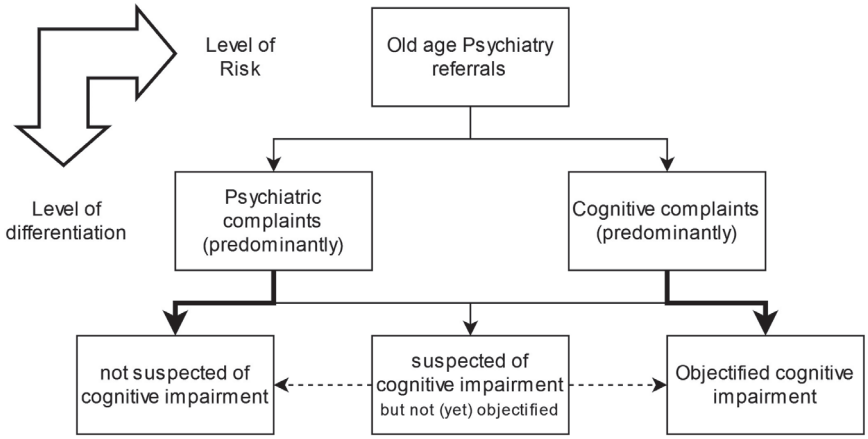

Figure 1. Levels of certainty of cognitive impairment in old age psychiatry and who to screen.

This results in different levels of selection for screening: screening all referred patients to old age psychiatry, or only those considered at high risk.

Screening all referred patients during an initial interview brings benefits in the form of knowing patients' cognitive status, besides avoiding doctor delays or patient delays. These benefits go beyond just (early) detection of cognitive impairment present at the time of the initial history interview that would otherwise be unnoticed. They can also help with issues in the near future such as foreseeable cognitive problems due to prevalence, psychotropic medication, or psychiatric episodes, among others. Of course, screening patients without complaints and at lower risk is not without a downside. The most prominent are the financial cost, psychological burden, and false positives, but all Wilson and Jungner's criteria apply. On the ethical side is the unexpected discovery of cognitive impairment with major social consequences for patients. The more the population that is screened is preselected

and is at an increased risk of cognitive impairment, the less this downside will be an issue. However, this preselection of the screened population comes with missing the benefits of screening all, next to the chance of missing unseen cognitive impairment.

In short, there are advantages and disadvantages of a screening. They depend on *why, when, where*, and who is being screened. And of course 'With *What*' are we going to screen is of significance, too.

1.5. What

1.5.1 What test do we use?

Cognitive complaints are a core feature of many (unmet) problems encountered in old age psychiatry and often remain hidden, deliberately or not, but have a major impact on the treatment and quality of life. Therefore we want or even need to know the cognitive state during the initial history interview of referred patients.

In 2008, I sought a substitute for the MMSE because it lacks the ability to detect MCI (Pinto *et al.*, 2019). As explained above, in old age psychiatry, we encounter a lot of subjective cognitive impairment due to various possible aetiologies that are not detectable by the MMSE. Therefore, this engenders the problem of not being able to objectify these complaints and follow their course. Were they too subtle to be detected or were the complaints only subjective? It is known that the MMSE cannot detect mild impairment well, as it is not designed to detect MCI. It was designed as a short and fast test for detecting major cognitive impairment. Part of the MMSE, a memory test, asks for three words to be remembered: the MoCA asks for five words. However, during an elaborate neurocognitive assessment, participants are asked to remember 15 words. The latter takes considerably more time, but no ceiling effect occurs, as the median number of words to remember is approximately six to seven. In addition, a learning effect can be observed, since the 15-word test is repeated more often. This example illustrates well the tension between trying to be fast and trying to be complete, limiting wrong conclusions. A bedside test that could objectively assess the cognitive state, including MCI, of our patients quickly, cheaply, conveniently, and sensitively enough to detect mild cognitive impairment, was needed. Among others, I considered the 2-minute test, 7-minute test, clock drawing test, ACE/ACE-R (Addenbrooke's Cognitive Examination), and the CAMCOG (in part). Because of an educated guess, I chose the newly introduced MoCA.

Montreal Cognitive Assessment 'MoCA':

The MoCA is a widely used short screening tool for MCI and mild dementia (MD). It was introduced and validated in French and English in 2005 (Nasreddine *et al.*, 2005). Until now, it has been validated in multiple settings and languages, although not in psychiatry (*mocatest.org*). It is now recommended by several institutions and guidelines, including Cochrane and Alzheimer International, to use it as a screener for cognitive impairment (Davis *et al.*, 2013; Alzheimer's disease International, 2016). Its use and popularity are growing fast, and it seems to be rivalling the MMSE. There are 867 publications to date (d.d. January 2022) with the MoCA as the main subject (mentioned in the title) and even several more using the MoCA in their study to measure cognition (9722 with MoCA as a keyword with Embase).

The MoCA consists of one page covering the cognitive domains of executive function and visuospatial abilities, naming, short-term memory, attention and working memory, language, concentration, verbal abstraction, and orientation. It can be performed within 10 minutes, with a maximum score of 30, indicating that no errors were made. Scores can be corrected for low education according to instructions by adding one point to the total score of patients with 12 years of education or less. Three validated versions differ from each other in minor ways to avoid a learning curve. The nature or subject of the questions remained the same, but the numbers or words differed between versions. For example, version one asks to subtract 7 from 100, whereas version 2 asks to subtract 6 from 100. The originally suggested cut-off for the diagnosis of cognitive impairment was a score of < 26 (less than 26). In the original study, the MoCA was compared to the MMSE. The results showed that it was superior to the MMSE in detecting MCI and mild AD. At a cut-off <26, the sensitivity of the MoCA was 90% for MCI and 100% for mild AD. This was 18% and 78% for the MMSE, respectively. The MoCA's specificity was 87% compared to 100% for the MMSE. Indicating that the MoCA was too difficult for 13% of the non-impaired, but the MMSE was too easy for 82% of the mildly impaired and 12% of the people with mild dementia.

However, the results of the Dutch version in patients with cognitive symptoms in a geriatrics department deviated from this for unknown reasons, with a sensitivity and specificity of 72% and 73% for MCI, respectively, compared to healthy controls (Thissen *et al.*, 2010). Validation has also been performed in several specific populations, including vascular dementia (Ihara *et al.*, 2013), frontotemporal dementia (Freitas *et al.*, 2012) and Alzheimer's disease (Freitas *et al.*, 2013).

Depending on the population in which the test is administered, reliability changes. The positive predictive value (PPV) decreases and the negative predictive value (NPV) increases when there are fewer cognitive impaired patients in the studied population. For example, for the MSSE in a memory clinic, the PPV is 86% and NPV is 73%, and in general practice, the PPV is 54% and NPV is 96% (Mitchell, 2009). A test should be validated for specific populations to maintain high reliability (Rossetti *et al.*, 2011). The reliability changes are partly due to the prevalence of the target disease in the population. However, as explained before, in old age psychiatry, the symptoms overlap more between the diseases and, therefore, it becomes more challenging for a test to identify the target condition. It should be noted that the MoCA tests a state and not a disease.

The original validation study (Nasreddine *et al.*, 2005) uses healthy controls for comparison. Although this is often done in validation studies, it is prone to introduce bias (Davis *et al.*, 2013; Bossuyt *et al.*, 2015). This will especially affect the specificity, as the comparison group will have clinically unrealistically high (good) MoCA scores. Healthy controls would normally not reach out for an assessment, as they are selected to have no cognitive complaints, impairments, or any other disease that could cause cognitive complaints. Therefore, separation from the impaired group will be too optimistic. This results in unnaturalistic high specificity. In clinical practice, an assessment should identify impaired patients in a naturalistic population, who, in our case, are patients that are referred (with complaints). If the MoCA is used for screening purposes, the setting (population) is of great importance. Healthy controls are seldom included in the target population.

There is since the MoCA was introduced more literature on the effects of the (study) population on cutoffs. Normative data are also available. In short, multiple studies have suggested that the original cutoff creates too many false positives, and the specificity is expected to be lower in a clinical setting (Davis *et al.*, 2015; Carson, Leach and Murphy, 2018; Elkana *et al.*, 2020). This was partly expected as it used healthy controls, but other parameters that influence MoCA scores have emerged besides education. The most prominent are age and social status (Pinto *et al.*, 2018).

Therefore, it is clear that the MoCA, as with other tests, should be validated in the setting and population where they are going to be used. In our case, one can debate whether this is for all referred patients to old age psychiatry or only for those suspected of having cognitive impairment.

Camberwell Assessment of Need for the Elderly 'CANE':

For finding the 'unmet needs' and 'needs' we used the CANE (Camberwell Assessment of Need for the Elderly) which has been validated already (Reynolds *et al.*, 2000).

The CANE is a semi-structured interview based on the Camberwell Assessment of Need (CAN) (Phelan *et al.*, 1995), which is adapted for the elderly. It was developed to 'measure the needs of people in the general adult population with severe mental illness. It is based on a model of need as a subjective concept, accepting that there may be differing but equally valid ideas about the existence of a need'. Therefore, the needs are not solemnly scored from the professionals' perspective, but also from the experience of the patient and (especially important for patients with cognitive impairment such as dementia) from the caretakers' perspective. This results in three different scores from three different points of view that can be compared. Where 'Identifying a need means identifying a problem plus an appropriate intervention which will help or alleviate the need' or 'a need was thought to be present when a patient's level of functioning falls below or was threatened to fall below, some minimum specified level and if a potentially effective remedy existed'. It consists of 24 questions covering 24 areas divided into 4 domains (environmental, physical, psychological, and social needs). Each of the 24 areas or 'items' is scored on a 3-point scale. This item or need can either be: no problem, that is, 'no need' (0 points); no/moderate problem because of continuing intervention, that is, 'met need' (1 point); and current serious problem, irrespective of any on-going intervention, that is, 'unmet need' (2 points). The duration of administration to the patient, next of kin, or clinician are 30, 20, and 10 minutes respectively.

1.5.2 What do we mean (definitions)?

The abovementioned personal clinical experience reveals multiple uncertainties. These uncertainties led to questions. We aim to reduce uncertainty of some (by no means all) of these questions by our study. However, before addressing these uncertainties, definitions must be introduced to avoid further confusion.

'Need':

In the paragraph above, the word 'need' was introduced. In general, a 'need' can be translated to, amongst others, *require (something) because it is essential or very important rather than just desirable* (*Google.com*, 2021) or *the things that a person must have in order to have a satisfactory life* (*Cambridge dictionary*). 'Need' in the context of well-being probably

reminds most readers of the Maslow pyramid (Maslow, 1954, 1970). In our study we use the definition of – and objectively define 'needs' by – the Camberwell Assessment of Needs for the Elderly (CANE). The CANE incorporates the Maslow findings as well as the taxonomy proposed by Bradshaw (Bradshaw, 1972) involving normative needs (by experts), felt needs (by patients), expressed needs (or demanded), and comparative needs (with other patients) from a sociological perspective. The aforementioned contemplations or dilemmas I experienced (in the *Why* paragraph) is well-described by the concepts presented in the dissertation of Reynolds (Reynolds, 2003) on the CANE that are: Need: What people benefit from; Demand: What people ask for; Supply: What is provided. How these three concepts are interpreted is prone to change over time for numerous reasons, but most noticeable to knowledge (of science, e.g. doctor, as well as the patients/public) and resources (in money as well as technics). The results of these three interpretations will have an effect on doctors' responses to the dilemma mentioned above, that is, when should a doctor (re)act even if a need is not expressed as such? This includes the question of whether screening is desirable. It is, therefore, not surprising that these three concepts (need, demand, and supply) are, to some extent, reflected in Wilson and Jungner's criteria listed above, although the criteria in themselves did not change over time. One could say that the questions remain the same, but the answers will change.

The DSM IV and DSM 5 list the diagnostic criteria for different psychiatric and neurocognitive diseases (NCD). Without trying to be complete but also trying not to copy the DSM, we will summarise and capture its essence here as an introduction with an emphasis on cognitive impairments.

'Mild cognitive impairment':

Mild cognitive impairment, often abbreviated as MCI, was (re)introduced by the Mayo clinic in 1999 and 2004 (Petersen, 2004). The definition of MCI has evolved over the years; however, the idea behind it remains the same (Table 2). The idea behind introducing MCI is that cognitive impairment is a state on a continuum ranging from normal cognition on one side to dementia on the other end of the continuum. 'It should be considered as a description of cognitive functioning in which the underlying disorder can vary rather than as a nosological entity representing the prodromal stage of AD' (Visser and Verhey, 2008). However, the original starting point of the concept focused on Alzheimer's disease (AD); therefore, the theory was more towards MCI being a state before the transition towards Alzheimer's disease. In recent decades, there has been a shift in awareness that, even though Alzheimer's disease is the most frequent cause of

dementia, dementia has multiple aetiologies. With this shift, the concept of MCI has also changed. From a prodromal or predementia concept of '*… a transitional period between normal ageing and the diagnosis of clinically probable very early AD, and this transitional zone has been described using a variety of terms such as mild cognitive impairment*' (Petersen, 2004) towards a more descriptive intermediate functional state to '*define the grey area between intact cognitive functioning and clinical dementia*' (Petersen *et al.*, 2014). With the emancipation of other aetiologies besides AD that can cause cognitive impairment, the criteria of MCI were also adapted. From primarily memory-focused criteria towards '*a condition in which individuals demonstrate cognitive impairment with minimal impairment of instrumental activities of daily living*' (Petersen *et al.*, 2018). Most importantly '*it can also be secondary to other disease processes i.e., other neurologic, neurodegenerative, systemic, or psychiatric disorders*' (Petersen *et al.*, 2018). With this shift, both cognitive and functional abilities must be considered in the evaluation of MCI (Winblad *et al.*, 2004). In turn, these adaptations initiated further specification of the MCI. This involves differentiating between amnestic (aMCI) or non-amnestic (naMCI) disorder and with or without multiple domains. This results in four subtypes: aMCI (single or multiple domains), naMCI (single or multiple domains) (Petersen, 2004). Although MCI is less AD-focused, AD is still a frequently suspected probable cause. This is reflected in new subtypes like 'MCI due to AD' or 'MCI supported with biomarkers', although they are mainly created for research purposes (on early interventions for AD) (Mattsson *et al.*, 2009). One reason for this is that not all patients with MCI develop dementia. Even more, there is substantial literature that 20% (up to 55% are reported) revert to normal cognition, 40% remain stable, and 40% convert to dementia. By creating subgroups of MCI, studies attempt to predict who is at a higher risk of developing dementia (Visser and Verhey, 2008). Although the percentages of reverting and converting differ substantially in the literature, it is acknowledged that people with MCI have a significantly higher risk of progressing to dementia than age-matched controls (Alexopoulos *et al.*, 2006; Petersen *et al.*, 2018). This difference in conversion rate as well as the prevalence and incidence that vary across studies is most likely due to the differences in study populations, as incidence increases with age and the type of patient (Visser and Verhey, 2008; Bermejo-Pareja *et al.*, 2021) — 5% to 15% for the annual conversion rate to dementia compared to 1–2% for controls, resulting in a five to ten times higher conversion rate. Cumulative dementia incidence was 14.9% in individuals with MCI older than age 65 years, during following 2 years.

MCI prevalence was 6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84 (Petersen *et al.*, 2018).

Table 2. Criteria for (M)CI over the years.

Original 1999 Mild Cognitive Impairment Criteria	**Recommendations General criteria for MCI 2004**	**Minor NCD DSM 5 2013**	**Major NCD DSM 5 2013**
-Memory complaint, preferably corroborated by an informant -Memory impairment documented according to appropriate reference values -Essentially normal performance in non-memory cognitive domains -Generally preserved activities	Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome) Cognitive decline: -Self and/or informant report and impairment on objective cognitive tasks -Evidence of decline over time on objective cognitive tasks and / or Preserved basic activities of daily living / minimal impairment in complex instrumental functions	Moderate Cognitive Decline • NOT Interfere with independence • Not due to delirium • Not due to other mental disorder	Significant Cognitive Decline • (minimal) interfere with independence in everyday activities (ADL) • requiring assistance with instrumental activities of daily living (IADL) • Not due to delirium • Not due to other mental disorder

ADL; activities of daily living. IADL; instrumental activities of daily living. NCD; neurocognitive disorder.

'Dementia':

I often tell my patients that dementia is not a disease but an agreement between doctors. It defines a cognitive state that can be caused by many different aetiologies, and more than 50 cases have been reported. However, a large majority of these causes are attributed to Alzheimer's disease (AD). Other common causes are vascular dementia, Lewy body dementia, and frontotemporal dementia. As always, we (the doctors) try to simplify things for our patients but not ourselves. Thus, there are many different agreements on what is considered dementia, but these agreements differ from each other. As our study was based on psychiatry, we used the DSM-IV, and later, the DSM 5 classification (the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000, 2013)) in the lead for dementia. However, we also incorporate the different classifications of different specialist or advocate groups per clinical disease, for example, NIA-AA/NINCDS-ADRDA for AD (McKhann *et al.*, 2011). The WHO describes dementia as 'a syndrome occurring as a result of disease of the brain, which is usually chronic or progressive in nature. It consists of impairment of several higher cortical functions, which include memory, thinking, comprehension, calculation, learning, language and judgement. These impairments often occur alongside changes in emotional control, social behaviour or motivation. Alzheimer's disease and cerebrovascular disease are among the causes of dementia'. In general, one could summarise the global concept of 'all-cause' dementia as 'the cognitive deficits are sufficient to interfere with independence

and show a decline (from a previous level), that is, requiring (minimal) assistance with instrumental activities of daily living (IADL)'.

These definitions attempt to create a theoretical yes or no situation or a sharp line on the cognitive continuum. However, in clinical practice, there is a grey area, or rather a rainbow, of interpretation differences. Attempts have been made to categorise this continuum. The DSM 5 uses the words '*modest*' versus '*substantial cognitive decline from a previous level of performance in one or more of the domains*' to capture the difference between not (yet) having dementia (minor Neurocognitive disorder (NCD)/MCI) and patients with dementia in words. An attempt to operationalize this is by stating '*test performance in the range of one and two standard deviations below appropriate norms*' for minor versus '*test performance in the range of two or more standard deviations below appropriate norms*' for major NCD. This translates to a score between the 3rd and 16th percentiles for minor NCD and below the 3rd percentile for major NCD, whereas the (amnestic) MCI was defined to have a delayed recall of 1.5 standard deviations below appropriate norms on a 15-word verbal learning test (Petersen *et al.*, 1999).

One method is to quantify the cognitive continuum by using severity or rating scales. The CDR (0-3) (Hughes *et al.*, 1982) and GDS (1-7) (Reisberg *et al.*, 1982) are the most well-known (Table 3). This is to (try to) objectify the staging of cognitive impairment/dementia and is used for multiple purposes such as research, renewal of the driving licence, and nursing home allocations.

Table 3. Rating scales for cognitive impairment.

	CDR Clinical Dementia Rating Scale		**GDS** Global Deterioration Scale
CDR0	No cognitive impairment	GDS1	No cognitive impairment
		GDS2	Age-associated impairment
CDR0.5*	Very Mild Dementia	GDS3	MCI
CDR1	Mild Dementia	GDS4	Mild Dementia
CDR2	Moderate Dementia	GDS5	Moderate Dementia
CDR3	Severe Dementia	GDS6	Moderate Severe Dementia
		GDS7	Severe Dementia

* *In clinical practice, CDR0.5 is often considered as equivalent to MCI but formally, it is already called dementia while this is an exclusion criterion for MCI*

Another factor in dementia diagnostics is to express the diagnostic certainty in terms of probability. This practice of the Alzheimer diagnostic guidelines of the NIA-AA/NINCDS-ADRDA (McKhann *et al.*, 2011) are spreading to other diagnostic guidelines. The additions

'possible' and 'probable' are most often used to quantify the amount of and/or core criteria met with respect to the classification guidelines with 'unlikely' and 'definite' (e.g., evidence of AD via autopsy or biopsy) on either side. These additions also represent well the specificity or uncertainty that these classifications still obtain.

Psychiatric symptoms in dementia, often expressed as behavioural and psychological symptoms of dementia (BPSD), are not only important in invalidating symptoms and lowering the quality of life, but they can also have a diagnostic and predictive role (Defrancesco *et al.*, 2020). '*Affective syndromes characterized by depressive symptoms are associated with faster functional decline whereas Manic syndromes are better at predicting cognitive decline*' (Palmer *et al.*, 2011). However, as up to 50% and 80% of the patients with MCI and dementia, respectively, exhibited (relevant) (neuro)psychiatric symptoms from the month of onset of the cognitive symptoms or the month prior to the diagnosis, these symptoms can not only have a predictive role but also mimic psychiatric diseases and frustrate the diagnostic process (Lyketsos *et al.*, 2002; Eikelboom *et al.*, 2021).

'Cognitive domains':

Cognitive impairment may occur in different forms or functions. These functions can be categorised into different domains. Again, how or where the functions are categorised can differ, depending on the literature. Most often, we distinguish attention, planning, inhibition, learning, memory, language, visual perception, spatial skills, social skills, and other cognitive functions.

In short, we follow the below (DSM-5) descriptions of the domains: complex attention, executive functions (attention, planning, inhibition), language, learning and memory, perceptual motor function (visual perception, spatial skills), and social cognition.

Table 4. DSM 5 descriptions of the cognitive domainds

Domains (DSM-5)	Description	Examples
Complex attention	involves sustained attention, divided attention, selective attention, and information processing speed	Trail making test Serial seven Digit span Months backwards
Executive ability	involves planning, decision making, working memory, responding to feedback, error correction, overriding habits, and mental flexibility	Proverb test Letter Fluency (phonemic)
Language	involves expressive language and receptive language	naming, fluency, grammar, and syntax repetition
Learning and memory	involves immediate memory, recent memory (free recall, cued recall, and recognition memory), and long term memory	Memory test of words (verbal memory) or pictures (visual memory)
Perceptual - Motor - Visual perception	praxis- Conception and planning of a motor act in response to an environmental demand	involves picking up the telephone, handwriting, using a fork/spoon Clock drawing test
Social cognition	involves recognition of emotions and behavioural regulation, social appropriateness in terms of dress, grooming, and topics of conversation	Recognizing emotions Theory of mind

Although the MoCA tests several domains, it does not test all of the above-mentioned cognitive domains. Below, we explain the cognitive domains used by the MoCA per item.

The instructions are read out aloud. There should not be any aid from the staff or from the next of kin. If a patient corrects their mistake (immediately) by themselves, the points to be gained will be allocated.

Table 5. The domains the MoCA tests and how.

Domains (MoCA) Max 30 points	**Description/ Item**	**MoCA test example** (V7.1)
Visuospatial and Executive functioning max 5 points:	With a pencil on the paper	
	Alternating Trail Making, 1 point	The patient is asked to draw a line alternating between numbers and letters in increasing order. The letters and numbers are scattered or 'not in an orderly placed' on the test field.
	Visuo-constructional Skills, 1 point	The patient is asked to copy a three-dimensional figure: a cube.
	Visuo-constructional Skills, 3 points	The patient is asked to draw a clock including the hands on ten past eleven. Points are scored for the shape (1), digits in order (1) and putting the hands in the correct place (1).

Domains (MoCA) Max 30 points	**Description/ Item**	**MoCA test example** (V7.1)
Language: max 6 points		
	Naming, 3 points	The patient is asked to name three figures (animals) that are not too familiar: a lion, rhinoceros, and a dromedary
	Repetition of sentences, total 2 points, 1 point per sentence	Two different sentences are read out aloud and the patient is asked to repeat them exactly as they were.
	Verbal fluency (letter), 1 point	The patient has to tell as many words as they can think of that begin with a certain letter in one minute time. No names, numbers, or suffixes are allowed.
Imprinting / Memory no points / 5 points		
	Imprinting, (no points)	A list of 5 words at a rate of one per second is read out aloud. The patient is asked to repeat them. The list is read a second time and again the patient is asked to repeat them. Thereafter, the patients will be asked to recall these words at the end of the test (approximately 10 minutes later).
	Delayed recall of the 5 words, Max 5 points	One point for each word recalled freely without any cues. Optional: more information (although without points to be gained) can be obtained by giving the patient a semantic category cue and later a multiple choice (3 options) when they can't remember a word spontaneously.
Attention: max 6 points		
	Forward Digit Span and *Backward Digit Span*, 2 points:	Five numbers are read out aloud and patients are asked to repeat them in the same order. Three numbers are read out aloud and patients are asked to repeat them in the reverse order *Serial 7,* 3 points: The patient is asked to subtract seven from 100, and then the patient is asked to keep subtracting seven from their answer up to five times.
	Vigilance/ Inhibition, 1 point:	The examiner reads the list of letters and the patient is asked to tap on the table only when a certain letter is mentioned.
Abstraction, max 2 points,	1 point to each item pair correctly answered	The examiner asks the subject to explain what each pair of words has in common. E.g., train and bicycle.
Orientation: Max 6 points		
	Time, 1 point per item	date, month, year, day of the week
	Place, 2 points	Location (building) and city

'Depression':

Overall, depression is a mood disorder that persists for more than two weeks. The main symptoms of depression are persistent feelings of sadness and loss of interest. In addition to these two symptoms, of which at least one should be present, there are seven additional symptoms. A total of five or more symptoms should be present for most of the day. One of these criteria is difficulty in thinking, concentrating, making decisions, and remembering things. It is consistent that cognitive impairment is common in depression and even more so in late-life depression. Up to 90% of depressed patients experience, According to the STAR*D study, some kind of cognitive difficulties (Rush *et al.*, 2006). This includes verbal processing, attention, learning, memory, and several aspects of executive functioning, including set-shifting, working memory, and response inhibition. It is debated whether cognitive impairment persists in patients with remitted depression (Grützner *et al.*, 2019; Semkovska *et al.*, 2019). Most of the cognitive impairment occurs during an episode and improves after patients recover from their depression (Roca *et al.*, 2015; Ahern and Semkovska, 2017; Grützner *et al.*, 2019). Although not all domains recover equally or fully, there seems to be a relationship with the number of episodes that someone has suffered (Roca *et al.*, 2015; Ahern and Semkovska, 2017; Riddle *et al.*, 2017; Semkovska *et al.*, 2019). Some studies have reported a less significant recovery (Ahern and Semkovska, 2017). For unipolar depression, deficits in selective attention, working memory, and long-term memory persist after remission and worsen with repeated episodes (Semkovska *et al.*, 2019). However, it is argued, especially in unipolar depression, that this is due to the inconsistency in clinical remission in these studies (Grützner *et al.*, 2019).

Among older depressed patients, up to 50% meet the criteria for MCI (O'Brien *et al.*, 2004). In the case of late-onset depression, it is suggested that it can be a prodromal sign of dementia (Lenoir *et al.*, 2011) and it is considered a risk factor for dementia. Patients with MCI and depression have a higher conversion rate than patients with MCI who are not depressed (Ma, 2020; Mukku *et al.*, 2021).

However, the opposite seems to be true as well. Dementia is considered a risk factor for developing depression, and up to 50% of patients with MCI and dementia have depression (Lyketsos *et al.*, 2002; Zhao *et al.*, 2016; Eikelboom *et al.*, 2021). Although the literature is not consistent with this prevalence, it is clear that it is higher than non-cognitive impairment (Ma, 2020).

'Bipolar disorder':

Bipolar disorder is a mood disorder characterised by well-recognizable episodes of extreme mood swings that include at least one episode of mania or hypomania (one week or longer of being euphoric, full of energy, or unusually irritable) and possibly depression. During a manic episode, there can be problems with attention and distraction that can translate into cognitive deficits. Cognitive difficulties are prone to exist due to distraction (hypervigilance and hypo-tenacity), high association, and other core features of mania, or in the case of a depressive episode, the opposite symptoms: apathy, low association, and disturbed vigilance and tenacity.

There are several types of bipolar disorder and its related disorders. These may include mania, hypomania, and depression. Symptoms can cause unpredictable changes in mood and behaviour, resulting in significant distress and difficulty in life.

Table 6. Different Bipoar disorder types.

Type	Description
Bipolar I disorder	The patient has had at least one manic episode, which may be preceded or followed by hypomanic or depressive episodes. In some cases, mania can lead to a break from reality (psychosis).
Bipolar II disorder.	The patient has had at least one depressive episode and at least one hypomanic episode, but never a manic episode.
Cyclothymic disorder	The patient has had at least two years (or one year for children and teenagers) of many periods of hypomania symptoms and periods of depressive symptoms (although less severe than depression).
Other types	These include bipolar and related disorders caused by certain medications (prednisone is the most notorious), drugs or alcohol or as a result of a medical condition, such as Cushing's disease, brain trauma, or stroke.

To date, no differences in cognitive impairment have been found between the clinical bipolar disorder subtypes bipolar type I and II (Bora, 2018). Hospitalisation, number of episodes, or psychosis do not seem, although debated, (significantly) associated with any particular cognitive domain in unipolar depression, as it seems to worsen executive function, working and verbal memory, and processing speed in bipolar depression (Bortolato *et al.*, 2015; Cardoso *et al.*, 2015; Bora, 2018). However, there is inconsistent or no evidence in longitudinal studies that cognitive impairment is progressive (Bortolato *et al.*, 2015).

The cognitive profile of bipolar disorder is similar to that of schizophrenia, but to a lesser extent (Van Rheenen *et al.*, 2017). The cognitive domains affected are widespread, and one cannot speak of a specific neuropsychological signature to differentiate the two (Bortolato *et al.*, 2015). As for euthymic patients compared to controls, there are noticeable differences

in the domains of attention, processing speed, (episodic) memory, executive functions, and verbal learning (Bortolato *et al.*, 2015). Patients in a manic state have additional impairment of verbal learning, as patients with depression show more phonemic fluency impairment. Patients with bipolar disorder show on average between 0.6 and 0.9 standard diviations on neuropsychological test, lower than that in healthy controls, with letter fluency and cognitive flexibility figuring prominently (Bortolato *et al.*, 2015).

'Schizophrenia':

Schizophrenia can present itself as a combination of delusions, hallucinations, and extremely disordered thinking and behaviour. The symptoms are present for at least six months (unless it is treated). Next to these 'positive' symptoms, there can be signs of 'negative' symptoms where the patient exhibits low activity and/or initiative and is not able to function normally.

The American Psychiatric Association describes that deficits in declarative memory, working memory, language function, executive functions, and processing speed can occur in schizophrenia. Cognitive symptoms are a core symptom of schizophrenia (American Psychiatric Association, 2013), which are often present before the first episode and persist after remission (Quisenaerts, Morrens and Sabbe, 2013; Bortolato *et al.*, 2015). Up to 70% of the patients will show cognitive impairment (O'Carrol, 2000). In addition to bipolar disorder, there is increasing evidence for the existence of cognitive within-group heterogeneity with clusters of severe impairment, mild-to-moderate impairment, and relatively intact cognitive functioning (van Rheenen 2017).

Often, general cognitive disorders are already visible, especially working memory and attention, before there are psychotic characteristics, and cause the well-known decrease in social functioning (Reichenberg, 2010). They even interact with daily living more than positive or negative symptoms (Green, Kern and Heaton, 2004). This can and will interact with diagnostic certainty. To make it more complicated, as we mentioned earlier, this is also true for the early BPSD signs that can appear before cognitive symptoms in neurodegenerative diseases (Lyketsos *et al.*, 2002).

In schizophrenia, cognitive impairment is often between one or two standard deviations or more in multiple domains (Bortolato *et al.*, 2015; Van Rheenen *et al.*, 2019), but the most frequently noted deficits are in the domains of working memory and attention.

There appears to be a modest association between positive symptoms and neuropsychological test outcomes (de Gracia Dominguez *et al.*, 2009). However, a link exists between cognitive disorders and general (social) functioning (O'Carrol, 2000).

Meta-analyses show that there are cognitive impairments across all domains but also that there is a large overlap with healthy controls on an individual basis. No specific schizophrenia profile was found. Although executive functions and memory feature prominently, working memory seems to be particularly affected: impaired digit span and especially, backward digit span (Nuechterlein *et al.*, 2008). The category fluency task, not part of the MoCA, would also be impaired (Bortolato *et al.*, 2015). The mentioned disorders are only found at the group level and cannot be translated to the individual test results due to the very diverse individual profiles.

'Doctors' delay':

This defines the time elapsed between the first visit to the doctor and the correct diagnosis. This term is often used for delays that can occur due to misdiagnosis or not (yet) finding the aetiologies. Not reporting the symptom (correctly), but only the complaints, can be due to doctors' delay as well as patient delay.

'Patients' delay':

This defines the time elapsed between the onset of the first symptoms and the visit to the doctor for this symptom. There can be conscious and unconscious reasons for not mentioning the symptoms. Often encountered reasons can be divided into three stages, 1) appraisal delay: the time the patient takes to appraise a symptom as a sign of illness; 2) illness delay: the time taken from deciding one is ill until deciding to seek professional medical care; and 3) utilization delay: the time from the decision to seek care until the patient goes to the clinic and uses its services (Safer *et al.*, 1979). This is especially true for older individuals with cognitive impairment, such as those accepting symptoms as part of ageing. Shame, denial, fear of diagnosis or consequences, fear of stigmatisation, or not wanting to complain are also noticed (Parker *et al.*, 2020).

1.6 How- Aim and outline of the dissertation

In the previous paragraphs, we have substantiated the necessity of this study. One needs to be aware of the 'needs' and especially the 'unmet needs' during treatment. Multiple factors cause doctors and patients to delay these 'needs'. Cognitive impairment can lead to a major 'need', especially in old age psychiatry. An elaborate neurocognitive assessment to weigh or estimate this need is not feasible for all patients. A bedside test that is fast, such as the MMSE, is often not sensitive enough to detect mild impairment.

An assessment is always a compromise between the quantity and quality required. The locus of balance depends on the target population and purpose of the test. The MoCA seems to be a sweet spot for screening cognition in old age psychiatry, but it needs to be validated for this specific setting and its multidimensional population.

If we revisit Wilson's criteria to see what is needed for a good screening, we have to conclude that some of the criteria are not yet optimally met in old age psychiatry in our opinion, especially regarding the MoCA. With our study, presented in the following chapters, we attempt to address some of these voids.

Criterion 1 *The disease to be detected must be a major health problem*. To whom? What is considered a problem and by whom? Loneliness and age-related illnesses, such as mild memory problems, are not considered diseases, but they have a major impact on quality of life. To what extent are these major health problems?

There are many hidden health problems or needs for patients in old age psychiatry. These are hidden for different reasons and for different stakeholders. However, being hidden from one person does not mean being equally hidden from another. These shortcomings and needs have different shapes. First, we aimed to understand these needs and unmet needs. Therefore, we had to determine what needs exist, whether they are treatable, what their impact is, and whether they are recognised as the same by all stakeholders involved. Therefore, we screened for patients' needs and the extent to which they were met.

In **chapter two**, we attempt to address these issues. What are the needs and unmet needs of the patient according to the said patient compared to his practitioner? This study was done specifically in a population of elderly patients with bipolar disorder. This group is known to be different from younger patients with bipolar disorder. In doing so, we looked at '*The care needs of older patients with bipolar disorder*'. Do those needs include the same items in older individuals as those in younger adults, and are they perhaps just more of the same? Alternatively, are they different needs altogether?

As mentioned in the paragraphs above and confirmed in Chapter two, cognitive impairment is a major issue in old age psychiatry, especially when doctors are not aware of its presence among patients either in the present or in the near future. It influences not only the patients' needs or quality of life but also the quality of treatment. Altered compliance was one of the most prominent in pharmacotherapy, as shown by the example in the *Why* section. Therefore, this dissertation focuses on cognitive impairment in old age psychiatry and how to make this more visible or aware, taking the Wilson and Jungner criteria into account.

Wilson and Jungner's Criterion 5: *A reliable detection method must exist* and criteria 9: *The cost of detection, diagnosis and treatment must be in an acceptable proportion to the cost of health care as a whole*. If we focus on cognitive impairment in the older adult psychiatry population, these two criteria together with criteria 6 (*The detection method must be acceptable to the public*) can conflict with each other, especially, but not solely, in old age psychiatry. This is because a comprehensive neurocognitive assessment has the highest reliability, but is next to being invasive for patients and exacting with respect to resources, to say nothing of the near future with a growing older adult population.

In the paragraphs above, we explained that an increasing number of people have cognitive complaints (e.g. MCI or dementia); they are mentioned and examined earlier in the process, which interferes with regular (psychiatric) treatments and diagnostics owing to increasing overlapping symptom presentation. A validated short test, which allows for a good interpretation of scores, can help identify or exclude mild cognitive impairment. The MoCA is becoming the standard in the world of short cognitive screening tests, rather than the MMSE. Internationally, the MoCA has been well validated. However, this is not the case with respect to Dutch. In addition, data on the MoCA in psychiatry and geriatric psychiatry, in particular, are lacking.

Although cognitive complaints are a core feature of many referral reasons encountered in old age psychiatry, it often remains unseen by patient delay or doctor delay, but it has a major impact on treatment, functional recovery, and quality of life. We introduced the MoCA during the initial history interview to determine the patients' cognitive state. Therefore, we need to study the MoCA and its criterion validity for screening for MCI and mild dementia in an old age psychiatric setting. In **chapter three,** *Diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) for cognitive screening in old age psychiatry: Determining cutoff scores in clinical practice. Avoiding spectrum bias caused by healthy controls.* We address the reliability of this short bedside test, the MoCA, which is cheaper, faster, and less demanding for patients and staff. However, is it reliable for screening all referred patients in an old age psychiatric setting?

The population or setting in which the test is used can significantly influence the performance of this test. As explained earlier, using healthy controls as comparisons improves the discriminating ability of the test. The opposite is true as well: by using comparisons that resemble the impaired, it will be harder for a test to discriminate. However, it will better represent the clinical reality. In **chapter four,** *Clinical value of the MoCA in patients suspected of cognitive impairment in old age psychiatry. Using the MoCA for triaging to a memory clinic*, we describe the reliability of the MoCA for triaging to a

memory clinic in an old age psychiatric setting, which is more the clinical setting for daily practice. Therefore, this study aims to validate the MoCA for patients suspected of having cognitive impairment in geriatric psychiatry. We will investigate whether the MoCA has sufficient discriminatory power for (the different underlying diagnoses with) MCI and more severe cognitive problems, and use patients suspected of but without objective cognitive problems as comparison group.

Criteria 4 and 10 '*There must be a recognizable latent or early symptomatic stage of the disease*' and '*The process of detection must be a continuous process and not a one-time project*'. The problem with criterion 4 is who is to be considered to have early symptomatic signs of mild dementia as MCI is on a functional continuum and dementia is a calcification or a definition from a nosological point. They are defined from a different perspective. This creates a subthreshold state in which not all individuals will convert to dementia. Taking into account the other criteria of Wilson, we present in this chapter an additional approach for screening with the MoCA using a double threshold. These criteria were examined for the probability of mild dementia and those at risk (MCI) in **chapter five,** *The MoCA with a double threshold: improving the MoCA for triaging patients in need of a neuropsychological assessment*.

Regarding Criteria 2 (*There must be a generally accepted method of treatment for the disease*) and 8 (*There must be agreement as to who should be treated*), '*treatment'* is translated to 'who is in need of an elaborate neurocognitive assessment'. With this in mind these criteria are examined in chapter five in particular and to a minor degree in the chapters 3 and 4 as well. Treatment should not only focus on the disease itself, but also on the problems or needs that arise from this disease. The needs that are unmet should attempted to be met, and this should also be considered a treatment.

The previous chapters elaborate more on theoretical starting points. **Chapter six** is an illustration of the added practical value of having performed a screening for cognitive impairment. This case study shows how an initial standard screening that seems to have no added value during the time of screening suddenly appears to contribute to saving someone's life.

Wilson and Jungner's Criteria 2, 3, and 7: '*There must be a generally accepted method of treatment for the disease*', '*There must be adequate facilities for diagnosis and treatment*' and '*The natural course of the disease to be detected must be known*' should be seen in a wider perspective and beyond the primary disease but include the needs caused by this disease. These issues are more generally debated in chapters three, four, and five and in more detail in the Discussion section (**chapter seven**).

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SECTION

Unseen needs

A


2
1988
R.Ravel

CHAPTER

The Care Needs of Older Patients with Bipolar Disorder

2

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ABSTRACT

Objectives:

With aging, bipolar disorder evolves into a more complex illness, with increasing cognitive impairment, somatic comorbidity and polypharmacy. To tailor treatment of these patients, it is important to study their needs, as having more unmet needs is a strong predictor of a lower quality of life.

Methods:

Seventy-eight Dutch patients with bipolar I or II disorder aged 60 years and older in contact with mental health services were interviewed using the Camberwell Assessment of Need in the Elderly (CANE) to assess met and unmet needs, both from a patient and a staff perspective.

Results:

Patients (mean age 68 years, range 61-98) reported a mean of 4.3 needs compared to 4.4 reported by staff, of which 0.8 were unmet according to patients and 0.5 according to staff. Patients frequently rated company and daytime activities as unmet needs. More current mood symptoms were associated with a higher total number of needs. Less social participation was associated with a higher total number of needs and more unmet needs.

Conclusions:

Older bipolar patients report fewer needs and unmet needs compared to older patients with depression, schizophrenia and dementia. A plausible explanation is that older bipolar patients had higher Global Assessment of Functioning scores, were better socially integrated and had fewer actual mood symptoms, all of which correlated with the number of needs in this study. The results emphasize the necessity to assess the needs of bipolar patients with special attention to social functioning, as it is suggested that staff fail to recognize or anticipate these needs.

2.1 Introduction

To date, 10-25% of bipolar patients are older than 60 (Sajatovic *et al*. 2005) and their absolute number will increase substantially in the coming years due to aging of the total population. Research on older bipolar patients is sparse and most existing knowledge is derived from studies in younger adults. However, bipolar disorder among the elderly is more complex with increasing cognitive decline (Schouws *et al.* 2010), somatic comorbidities (Lala and Sajatovic 2012) and polypharmacy (Dols *et al.* 2014). In addition, older bipolar patients receive less social support (Beyer *et al.* 2003), and are more dependent on informal care (Keith *et al.* 1971). To tailor the treatment of older bipolar patients and to optimize their general wellbeing, their needs should be studied. Needs assessments help to highlight specific areas on which health and social services can concentrate their efforts (Reynolds *et al.* 2000). Meeting unmet needs may lead to a substantial decrease in health expenses (Slade *et al.* 1999) and is regarded as an essential condition to improve health, wellbeing and quality of life of older people (Field *et al.* 2002). Disagreement between patients and staff on needs may influence compliance (Stobbe *et al.* 2013) and hence the experienced quality of treatment (Hancock *et al*. 2003; Slade *et al.*1999). Therefore a needs assessment preferably includes views from the patient and the professional caretaker (staff). Reports on needs of older bipolar patients by patients and staff are currently lacking. Studies in older psychiatric patients show that the number of needs is associated with the level of psychiatric and social functioning (Hancock *et al.* 2003; Houtjes *et al*. 2011; Kaiser *et al.* 2010; Meesters *et al.* 2013; Passos *et al.* 2012; Sultan *et al*. 2011; van der Roest *et al.* 2008; Walters *et al.* 2000), quality of life (Bengtsson-Tops and Hansson 1999; Slade *et al.*1999) and motivation for treatment (Stobbe *et al.* 2014).

Our aim was to investigate the needs of patients with bipolar disorder aged 60 years and over from the patient's and staff's perspective, using the Camberwell Assessment of Need for the Elderly (CANE) (Reynolds *et al.* 2000). We examined the number of needs, to what extent they were met, and how they related to several patient characteristics. We hypothesized that patients who report more needs, both met and unmet, have more mood and cognitive symptoms, a lower quality of life, and are less socially integrated.

2.2 Methods

2.2.1 Study sample

We identified all patients aged 60 years and older who were in contact with mental health services between 1 January and 31 December 2012, through a search of the computerized patient record system of the mental health institution GGZ inGeest, which offers outpatient and inpatient mental health services in two districts in Amsterdam, The Netherlands.

Patients were included if they met the selection criteria of having bipolar I disorder, bipolar II disorder or bipolar disorder not otherwise specified (NOS) of the diagnostical and statistical manual of mental disorders IV text revised (DSM-IV–TR (American Psychiatric Association 2000)). Exclusion criteria were the inability to provide written informed consent due to inability to communicate, intellectual disability (IQ below 70), poor cognition (Mini Mental State Examination (MMSE) < 18 (Folstein *et al.* 1975)), or current compulsory admission. The study was approved by the Medical Ethics Committee of VU University Medical Center, Amsterdam, The Netherlands.

Medical records of 139 potential participants were screened for exclusion criteria by a psychiatrist in accordance with local regulations before contacting patients to request consent. Eligible patients were asked by their psychiatrist to provide written informed consent for participation in the study. Inclusion diagnosis and additional psychiatric diagnoses were confirmed through the Mini-International Neuropsychiatric Interview Plus (MINI) (Sheehan *et al.* 1998). The psychiatrist who was treating the patient during the study period administered the MINI.

Of a total of 139 patients screened, 25 were excluded (Figure 1). Of the 114 eligible patients, 78 (fully participating) were able and willing to provide written informed consent and another 23 (partially participating) patients restricted consent to a review of their medical records.

To assess the needs we used the CANE (Reynolds *et al.* 2000) as it is commonly employed (Hancock *et al.* 2003; Houtjes *et al.* 2011; Iliffe *et al.* 2004; Kaiser *et al*. 2010; Meesters *et al.* 2013; Passos *et al.* 2012; Sultan *et al*. 2011; van der Roest *et al*. 2008; Walters *et al*. 2000) to assess the separate points of view of patients and staff and reveal unknown differences. The caregivers perspective in the CANE was not included as the majority of patients did not consent for a caregiver's interview.

2.2.2 Measurements

Demographic data (Table 1) were derived from patients' medical records and confirmed during the interviews. The age of onset was obtained from the MINI interview. The duration of illness was calculated as the number of years since the first mood episode fulfilling DSM-IV criteria. The Global Assessment of Functioning (GAF) scores (American Psychiatric Association, 2000) were reported by the patient's psychiatrist.

The Young Mania Rating Scale (YMRS) (Young *et al.* 1978) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977) were used to evaluate mood symptoms.

The YMRS consists of 11 items and is based on clinical observations and the patient's subjective report of the last 48 hours, measuring manic symptoms on a scale from 0 to 60. A score ≥ 7 is considered indicative of clinically relevant (hypo)mania. The CES-D measures the presence of depressive symptoms during the previous week, with a scoring range of 0 to 60. A score ≥ 16 is considered indicative of clinically relevant depression in the general population. Patients with scores below the threshold on both the YMRS and the CES-D were considered to be in symptomatic remission.

The MMSE (Folstein *et al.* 1975) was used to screen for cognitive impairment.

Self-reported limitations in activities of daily living were evaluated through the Groningen Activity Restriction Scale (GARS) (Kempen *et al.* 1996), which includes 11 activities of daily living (ADL) items and 7 instrumental activities of daily living (IADL) items. Scores were dichotomized into independent performance versus performance only with someone's help, resulting in a total score ranging from 18 (independent for all items) to 36 (dependent for all items).

Social integration was defined by network size and social participation. To assess the size of their social network, patients were asked to estimate the number of persons, outside of their household, with whom they had regular and meaningful contact. In addition, they were asked if they had an unpaid informal carer for at least one hour per week. Information was gathered on the presence of persons in their proximity, besides their partner, who they experienced as being emotionally or materially supportive. Self-report of involvement in 11 social activities (e.g., visiting others, going to church) was measured through the Social Participation Scale (Depla *et al.* 2003), with scores ranging from 0 (no activities) to 22 (regular participation in all activities).

Quality of life was evaluated with the Manchester Short Assessment of Quality of Life (MANSA) (Priebe *et al.* 1999), which rates patient satisfaction with various aspects of life (e.g., daily activities and physical health). The MANSA score is the mean of the 12 individual item scores, ranging from 1 (very dissatisfied) to 7 (very satisfied).

Needs for care were assessed with the Dutch version (Dröes *et al.* 2004) of the CANE (Reynolds *et al.* 2000) by interviewing both the patient and a staff member who knew the patient well. A total of 15 staff members were interviewed as a number of the participating patients shared the same staff member. The CANE is a semi-structured interview, based on the Camberwell Assessment of Need (CAN) and adapted for the elderly, that covers 24 areas (Table 2) of the four domains of environmental, physical, psychological and social needs, and has good validity and reliability (Reynolds *et al.* 2000; van der Roest *et al.* 2008). Each of the 24 items can

be rated on a 3-point scale: 0, 'no problem´ i.e. no need; 1, 'no/moderate problem because of continuing intervention´ i.e. met need; and 2, ´current serious problem, irrespective of any on-going intervention´ i.e. unmet need. The few cases where patients (N=21; 1.1 %) or staff (N=31; 1.6%) indicated that they did not know whether a need in a certain item existed the need was assigned 'no need' as no need was evident, to rate needs conservatively.

2.2.3 Statistical analysis

Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 20.0; SPSS Inc., Chicago, IL). A significance level of 5% was applied.

Differences between fully participating and partly participating patients were analysed with chi-square (χ^2) statistics for categorical variables and a Mann-Whitney U tests for age, as age was considered not to be distributed normally.

The frequency distributions of met and unmet needs, according to patient and staff, were determined. Comparisons between the total number of needs as rated by the patient and staff were performed with the Wilcoxon matched pairs signed-rank test, because the data were ordinal and skewed. To evaluate agreement on the presence of a need between patient and staff, Cohen Kappa coefficients (κ) were calculated. κ values between 0-0.20 indicate poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 very good agreement. The percent agreement calculation was also documented, by dividing the number of cases in which both patients and staff agreed that there was a met or an unmet need by the total number of needs.

Correlations between the patients characteristics and the number of needs was tested using the Spearman's rank-order test. A Spearman's rank correlation coefficient (rho) can vary between +1 and -1 (a perfect positive or negative correlation between the ranking of the two variables). There is no correlation with a coefficient of zero.

2.3 Results

2.3.1 Demographic and clinical characteristics

The mean age of fully participating patients was 68.9 years (SD=7.8, range 61–98), and 51.3% were male (Table 1). Our sample had a balanced representation of bipolar I and II patients, predominantly with an onset of illness before age 50. Relevant current mood symptoms were present in 31 patients (40%), 14 with (hypo)manic symptoms (YMRS $\geq$7) and 21 with depressive symptoms (CES-D $\geq$16), including 3 patients with scores above threshold on both scales. Only a few patients had a very small network size (8%).

Table 1. Characteristics of the Patient Sample (N=78)

Demographic data	
Age, means (SD), years/range	68.5 (7.8) 60-98
Gender, male (%)	40 (51)
Marital status, actual partner (%)	44 (56)
Parental status, has children (%)	55 (70)
Residence, n (%)	
Independent	69 (88)
Dependent	9 (11)
Hospitalized at time of study	0
Education, n (%)	
Low	9 (11)
Middle	26 (33)
High	43 (55)
Currently working	21 % now, 2.4% never
Income, monthly[1] n (%)	
<€ 800	15 (19)
€800 – 1200	12 (15)
>€1200	49 (63)
Clinical data	
DSM-IV	
Bipolar-I (%)	42 (54)
Bipolar-II (%)	36 (46)
Age of onset	
Early (<50 years)(%)	63 (81)
Late (50+)(%)	15 (19)
First episode depression (SD) [2]	32.8 years of age (14.5)
First episode mania (SD)	39.9 (16.4)
Duration of illness, mean (SD), years	35.1 (14.3)
Symptomatic remission (%)	47 (60)
GAFp (SD)	65.0 (11.2)
CES-D mean (SD) median (25-75%)	11.80 (10.3) 8 (3 – 17.5)
GARS mean (SD) median 25%-75%)[3]	23.01 (8.74) 19 (18- 24)
MMSE mean (SD), median (25%-75%)	27.73 (2.06) 28 (26-29)
YMRS mean (SD) median (25-75%)	4.90 (6.2) 3 (1- 6)
Social domain	
Network size n (%)	
0-1 person	6 (8)
2-5 persons	32 (41)
6 or more persons	40 (52)
Has informal carer. Yes (%)	46 (59)
Has confidant/supportive person. Yes (%) besides partner[3]	64 (82)
Social Participation Scale score, mean (SD)[3]	11.5 (3.3) 12 (9.5-14)
Quality of life	
MANSA total score, mean (SD)	61.9 (8.2) 5.2 per item

[1]2 cases missing

[2]11 cases missing

[3]1 cases missing

GAFp, Global Assessment of Functioning; CES-D, Center for Epidemiologic Studies Depression Scale; GARS, Groningen Activity Restriction Scale; MMSE, Mini Mental State Examination; YMRS, Young Mania Rating Scale; MANSA, Manchester Short Assessment of Quality of Life;

2.3.2 Assessment of needs

Patients reported a mean total needs of 4.31 (SD 3.48, range 0-17) which was similar to the total number of needs rated by staff (4.44 needs, SD 3.56, range 0-14, Wilcoxon z=-0.359, N=78, p=0.720, Table 2). The mean number of met needs rated by patients (mean 3.50, SD 2.81, range 0-14) and staff (mean 3.95, SD 3.18, range 0-12) were also comparable (Wilcoxon z=-1.702, n=78, p=0.089, Table 2). The mean number of unmet needs, however, was rated significantly higher by patients (0.81, SD 1.23, range 0-6) than by staff (0.49, SD 0.91, range 0-4, Wilcoxon z=-2.497, n=78, p=0.013).

No unmet needs were reported by 56.4% (n=44) of the patients and by 69.2% (n=54) of staff. According to the patients, 19% of their reported needs were unmet while according to staff this was 11%. Patients rated the proportion of their needs as unmet considerably higher in the psychological (22%) and social (35%) domains, as compared with staff (9% and 16%). In the other domains the ratings were comparable between patients and staff (12 versus 16% and 10 versus 8%), (Table 2). With regard to individual needs, household skills, physical health, medication and psychological distress were the most frequently rated met needs, both by patients and staff. The most frequently reported unmet needs rated by both patients and staff were company and daytime activities.

The percent agreement calculation between patients and staff was high (84.1%), with the lowest for company (62.8%), followed by medication (62.9%), physical health (65.6%), psychological distress (73.1%) and daytime activities (75.9%). The Cohen's kappa coefficient agreement between patients and staff rating was moderate (mean κ 0.45, SD=0.21). Poor agreement between patient and staff was found for needs regarding behavior, intimate relationships, and company ($\kappa < 0.2$).

Table 2. Ratings of Need In Individual CANE Areas and Total Number of Needs, According to Patient and Staff

Domains	Needs	Patient: Met Needs, N (%)	Staff: Met Need, N (%)	Patient: Unmet Need, N (%)	Staff: Unmet Need, N (%)	Agreement (%)	Kappa
Enviromental							
Accommodation		11 (14)	14(18)	2(2.6)	1(1.3)	88.4	0.617
Household skills		30 (38)	26(33)	1(1.3)	1(1.3)	85.9	0.705
Food		15(19)	14(18)	2(2.6)	3(3.8)	96.1	0.891
Money		8(10)	8(10)	3(3.8)	2(2.6)	92.3	0.679
Benefits		8(10)	5(6.4)	3(3.8)	1(1.3)	91.0	0.551
Caring for others		4(5.1)	5(6.4)	3(3.8)	2(2.6)	92.4	0.540
Total Enviromental		*76*	*72*	*14*	*10*		*0.664*
Physical							
Physical health		27 (35)	30(38)	5(6.4)	4(5.1)	65.6	0.541
Medication		25(32)	30(38)	1(1.3)	1(1.3)	62.9	0.217
Eyesight/hearing		16(20)	8(10)	5(6.4)	2(2.6)	80.8	0.435
Mobility		15(19)	15(19)	0(0.0)	1(1.3)	92.3	0.760
Self-care		8 (10)	11(14)	0 (0.0)	1 (1.3)	92.3	0.660
Continence		12(15)	6(7.7)	1(1.3)	0(0)	88.5	0.473
Total physical		*103*	*100*	*12*	*9*		*0.514*
Psychological							
Psychological distress		20(25)	23(29)	4(5.1)	0 (0)	73.1	0.383
Memory		11(14)	17(22)	3(3.8)	0 (0)	79.5	0.374
Behavior		4(5.1)	4(5.1)	0(0)	3(3.8)	88.5	0.138[1]
Alcohol		6(7.7)	12(15)	3(3.8)	3(3.8)	87.2	0.529
Deliberate self-harm		2(2.6)	3(3.8)	1(1.3)	0(0)	94.9	0.311
Accidental self-harm		5(6.4)	3(3.8)	1(1.3)	1(1.3)	91.0	0.262
Psychotic symptoms		6(7.7)	11(14)	3(3.8)	0(0)	82.0	0.217
Total psychological		*54*	*73*	*15*	*7*		*0.316*
Social							
Company		8(10)	19(24)	10(13)	4(5.1)	62.8	0.127[1]
Intimate relationships		1(1.3)	10(13)	3(3.8)	3(3.8)	82.1	0.130
Daytime activities		13 (17)	19(24)	5(6.4)	5(6.4)	75.9	0.454
Information		15(19)	12(15)	3(3.8)	0(0)	78.2	0.318
Abuse/neglect		3(3.8)	3(3.8)	1(1,3)	0(0)	94.9	0.406
Total social		*40*	*63*	*22*	*12*		*0.287*
Total							
	Mean (SD)	3.50 (2.81)	3.95 (3.18)	0.81 (1.23)	0.49 (0.91)	84.1	0.45 (0.21)
	Range	0-14	0-12	0-6	0-4		0.13-0.90

Note:

N =78

In italic are domain results

*K*appa values between 0-0.20 indicate poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 very good agreement

[1] p= > 0.05, meaning kappa is not significant different from 0

2.3.3 Correlations between needs and patient characteristics

The level of psychic functioning (GAFp) showed a negative correlation with the total number of needs rated by patients (r= -0.41) and staff (r= -0.47), and hence patients with less overall psychic functioning showed more total needs. Patients with current mood symptoms had a higher total number of needs: for depressive symptoms (CES-D), both according to the patients (r= 0.42) and their staff (r= 0.24), and for mania symptoms (YMRS) only according to the patients (r= 0.24). Patients with worse cognitive functioning (MMSE) had a higher total number of needs, according to both the patients (r= -0.46) and staff (r= -0.34).

Age was positively correlated with the total number of needs reported by staff (r= 0.30), but not with the total number of needs reported by the patients (r=0.17). Social participation was negatively correlated with the total number of needs (r= -0.31, r= -0.37) and unmet needs (r= -0.27, r= -0.33) reported by both patients and staff. Quality of life (MANSA) was negatively correlated with the number of total needs (r= -0.49, r= -0.34) and unmet needs (r= -0.33, r= -0.26) reported by both patients and staff. Thus patients with less social participation or quality of life had more total needs and unmet needs. Patients with a smaller network size had more total needs according to patients (r=-0.29) and staff (r=-0.25), and unmet needs according to patients (r=-0.26).

All these correlations were statistically significant ($p < 0.05$ Table 3).

Table 3. Spearman's Correlations of patient Characteristics With Total Numbers of Unmet and Total amount of Needs, According to Patients and Staff (N=78)

Variable	Patient		Staff	
	Unmet	total	unmet	total
	rho p	rho p	rho p	rho p
Clinical				
Age	0.016 p=0.886	0.166 p= 0.145	0.161 p=0.158	**0.297** **p=0.008**
MMSE	-0.163 p=0.154	**-0.461** **p<0.001**	-0.129 p=0.260	**-0.336** **p=0.003**
GAFp	**-.244** **p=0.031**	**-.412** **p<.001**	-.120 p=0.293	**-.468** **p<0 .001**
CES-D	0.181 p=0.112	**0.420** **p<0.001**	0.049 p= 0.671	**0.240** **p= 0.034**
YMRS	0.142 p=0.216	**0.235** **p=0.038**	0.062 p=0.588	0.153 p=0.181
Social				
Networksize	**-0.260** **p=0.021**	**-0.292** **p=0.009**	-0.128 p=0.266	**-0.246** **p=0.030**
Social participation	**-0.269** **p=0.017**	**-0.307** **p=0.006**	**-0.332** **p=0.003**	**-0.365** **p=0.001**
MANSA	**-0.334** **p=0.003**	**-0.494** **p<0. 001**	**-0.257** **p=0.024**	**-0.343** **p=0.002**

Note: In bold are the correlations that are statistically significant.

MMSE, Mini Mental State Examination; GAFp, Global Assessment of Functioning; CES-D, Center for Epidemiologic Studies Depression Scale; YMRS, Young Mania Rating Scale; MANSA, Manchester Short Assessment of Quality of Life;

2.4 Discussion

Our cohort of older patients with bipolar disorder had most of their needs in the items of household skills, physical health and medication. This is in accordance with the literature on older patients and their needs using the CANE (Arvidsson 2001; Hancock *et al.* 2003; Meesters *et al.* 2013; Walters *et al.* 2000). These needs were acknowledged by the staff and mostly met. However, a number of unmet needs were underestimated by staff, especially in the social domain, resulting in one out of five reported needs rated as unmet. These findings are in line with the Cohen's Kappa, all of the good to very good strength items ($k>0.6$) were situated in environmental and physical domains, whereas most of the psychological or social items had a poor to fair strength ($k<0.4$). Although the absolute number of unmet needs was low, it does require the attention of staff since unmet needs impair quality of life (Field *et al.* 2002; Stein *et al.* 2014), change the motivation for treatment (Stobbe *et al.* 2014) and raise the number of contacts with

professional carers (Goossens *et al.* 2007). Knowing these unmet needs allows for a well informed decision to either invest in countering the identified unmet needs or not. We compared our data with two studies on the needs of older patients with schizophrenia (mean age 69) (Meesters *et al*. 2013) or unipolar depressive disorder (mean age 72) (Houtjes *et al.* 2011). The schizophrenia patients reported a higher number of both total needs (7.57 versus 4.31 in our study) and unmet needs (1.46 versus 0.81 in our study). This may be explained by the fact that older patients with bipolar disorder had higher mean GAF scores (48.2 versus 65 in our study), fewer depressive symptoms (CES-D score 15 versus 8 in our study), a larger social network and higher social participation score (9.2 versus 11.5), and a better quality of life (MANSA 4.8 versus 5.2 in our study). Fewer psychiatric symptoms and better social functioning corresponded with a lower number of unmet needs in both studies. The older patients with unipolar depressive disorder had even more unmet needs (2.3) (Houtjes *et al.* 2011), possibly because of higher rates of depressive symptoms.

These studies on older patients with depression and schizophrenia underscore our hypothesis that patients with more psychiatric symptoms report more needs. This is not surprising, however it is important to point out that symptoms and needs maybe interrelated; symptoms may require help and therefore induce needs, but unmet needs may induce symptoms. Patients in our bipolar sample had fewer current psychiatric symptoms and less social impairment. This may be explained by the fact that bipolar patients, especially when using lithium as a long-term maintenance treatment, are recommended to remain in psychiatric care even when stable, thus enabling us to include both euthymic and symptomatic patients. Another aspect could be that bipolar patients only episodically have severe symptoms. Differences in accessibility and structure of healthcare could not explain our findings in older patients, as all studies were situated in the Netherlands. A study using the Camberwell Assessment of Need Short Appraisal Schedule (CANSAS) in younger adults with severe mental illness reported similar findings as our study. The subgroup of patients with bipolar disorder had significantly higher recovery and higher empowerment scores than the subgroup of patients with schizophrenia or depressive disorder and fewer needs unmet (Lloyd *et al.* 2010).

Studies on the needs of patients with dementia using the CANE reported a higher number of needs, respectively 10.3 and 10.2 (van der Roest *et al*. 2008; Kaiser *et al.* 2010). Lower cognitive functioning (mean MMSE 20 and <18 respectively) could explain the higher number of total needs in these studies, in line with our findings. Presumably, people with lower cognitive functioning usually have higher physical and functional dependency and need for support

with activities of daily living. The findings among residential home individuals (van der Ploeg *et al.* 2013) further support this as individuals diagnosed with dementia reported more needs compared to individuals without dementia in the same setting.

Other studies in mixed older psychiatric populations (Hancock *et al.* 2003; Passos *et al. 2012; Slade et al. 1999; Sultan et al. 2011)* reported more needs and more unmet needs than our study. As patients with bipolar disorder were a minority in these studies, factors other than psychiatric diagnoses could explain these differences. Although the number of needs, and particularly unmet needs, was higher in a study including patients 75 years of age and older (mean age 81.5) attending a general practitioners office (GPO) (Walters *et al.* 2000), there was no correlation between the number of needs with age in our and other studies (Lloyd *et al.* 2010). A study of Stein *et al.* (2014) among older patients (mean 80 years, range 68-98) from GPO without severe illness or dementia (mean MMSE 27), support our findings as their needs were less than in our study with respectively 2.51 needs and 0.25 unmet needs. This suggests that age is not a major contributor to the needs, however the literature is contradictive on this matter.

In our study the number of unmet needs correlated with a lower quality of life and poorer social participation. Company and daytime activities were the most frequently reported unmet needs by both patients and staff suggests that efforts aimed at improving social functioning of older patients with bipolar disorder are warranted and may result in better quality of life and fewer needs. As these results were also found in a study of relatively healthy elderly primary care patients (Stein *et al.* 2014), the findings appear to be independent of diagnosis and suggest a key role for social and emotional support. Generally, staff are aware that patients with more psychiatric symptoms have more needs. As psychiatric symptoms are usually the core focus of treatment, the staff may anticipate these specific needs. Needs regarding social functioning may be equally important from the patients' view but appear to be noticed or fulfilled less by staff. Good social functioning is important for quality of life (Valtorta and Hanratty 2012) in general, not just for psychiatric patients. One can debate whether social functioning of psychiatric patients is the sole responsibility of mental health organisations or a joint responsibility with public health organisations and politics.

The results of our study should be considered in the light of several strengths and limitations. To the best of our knowledge, for the first time, the met and unmet needs of older bipolar patients from the perspective of the patients and staff were systematically investigated. A strength of the study is that only one patient was excluded from the study

because of severe psychiatric symptoms. Although we found no significant differences between the fully participating (N=78) and partially participating (N=23) patients in demographic and clinical characteristics, the patients participating in the CANE had higher GAF score (65 (SD=11.15) versus 58 (SD 9.94) for patients not participating in the interviews (Mann Whitney U test (Z=-2.671, p=0.008) (data not shown)). This is a possible limitation, as we found a negative correlation with the total number of needs.

In our study we only included patients using specialised mental health services. Stable older patients with bipolar disorder may be treated by their family doctor or psychiatrist in a private practice (ten Have M. *et al.* 2002), and these patients probably have less complex disorders with fewer needs. On the other end of the spectrum, patients who refuse care are likely to be the most seriously ill. Despite these limitations, it must be noted that our findings are probably indicative for the large majority of older bipolar patients, as our institution is the sole mental health institution in these two districts and there are no financial barriers to receive health care.

2.5 Conclusions

Current mood symptoms, smaller network size, less social participation and lower cognitive functioning were associated with a higher number of needs reported by both patients and staff. It is striking that only social functioning correlated with unmet needs. A plausible explanation is that staff are aware of the correlations between needs and psychiatric symptoms but seem to fail to recognize or anticipate on needs in social functioning. Even though one can dispute if the social domain is the primary territory of psychiatric care, it seems indisputable that unmet needs in social functioning affect psychiatric health. It is therefore recommended that, psychiatric services acknowledge the patient ‘s needs in the social domain and evaluate if aid in this domain can be provided.

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SECTION

The MoCA validation in different old age settings

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CHAPTER

3

Diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) for cognitive screening in old age psychiatry: determining cut-off scores in clinical practice. Avoiding spectrum-bias caused by healthy controls

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International Journal of Geriatric Psychiatry 2020 Mar; 35(3):261-269.

doi: 10.1002/gps.5227

ABSTRACT

Objectives:

The Montreal Cognitive Assessment (MoCA) is an increasingly used screening tool for cognitive impairment. While it has been validated in multiple settings and languages, most studies have used a biased case-control design including healthy controls as comparisons not representing a clinical setting.

Methods:

The purpose of the present cross-sectional study is to test the criterion validity of the MoCA for MCI and mild dementia (MD) in an old age psychiatry cohort (*n*=710). The reference standard consists of a multidisciplinary, consensus-based diagnosis in accordance with international criteria. As a secondary outcome the use of healthy community dwelling older adults as additional comparisons allowed us to underscore the effects of case-control spectrum-bias.

Results:

The criterion validity of the MoCA for cognitive impairment (MCI+MD) in a case-control design, using healthy controls, was satisfactory (AUC 0.93; specificity of 73% <26), but declined in the cross-sectional design using referred but not cognitive impaired as comparisons (AUC 0.77; specificity of 37% <26). In an old age psychiatry setting the MoCA is valuable for: confirming normal-cognition (≥26, 95% sensitivity), excluding MD (≥21;NPV 98%) and excluding MCI (≥26;NPV 94%); but not for diagnosing MD (<21;PPV 31%) or MCI (<26;PPV 33%).

Conclusions:

This study shows that validating the MoCA using healthy controls, overestimates specificity. Taking clinical and demographic characteristics into account, the MoCA is a suitable screening tool – in an old age psychiatry setting – for distinguishing between those in need of further diagnostic investigations and those who are not, but not for diagnosing cognitive impairment.

3.1 Introduction

The Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) was developed as a brief screening test for Mild Cognitive Impairment (MCI). It is widely used across the world in a variety of settings (*mocatest.org*, no date). The MoCA is recommended by the Alzheimer's Society to objectively assess cognitive complaints in a clinical setting (Ballard *et al.*, 2015).

Even though more and more advocacy groups or policy makers favor screening for dementia there is still a debate if screening in various populations is wise(Borson *et al.*, 2013; Brunet *et al.*, 2013; Lin *et al.*, 2013; Prince and Comas-Herrera, 2016; Chambers, Sivananthan and Brayne, 2017; Burn *et al.*, 2018). However, the setting of old age psychiatry is different to our opinion. By knowing a patient's cognitive functioning at referral, besides timely detecting dementia also to monitor all causes of MCI in old age psychiatry, one can adapt their (psychiatric) treatment; e.g. pharmacotherapy (including compliance) or psychotherapy. Especially as this population is at greater risk of changing cognitive functioning not only by age but also by (psychotropic) medication or because of the referral reasons (Dautzenberg *et al.*, 2018; Volksgezondheidenzorg.info, 2019). In the Netherlands, referrals to old age psychiatry consist of a mix of neurodegenerative and other psychiatric disorders, such as depression, bipolar disorders, schizophrenia, and severe anxiety disorders, all of which can be accompanied by poor cognitive functioning (American Psychiatric Association, 2000; Bierman *et al.*, 2005; Schouws *et al.*, 2012; Baune and Renger, 2014; Bora and Pantelis, 2015).

We introduced in our clinic a short cognitive assessment using the MoCA for all referred patients to lower doctors delay by adding an objective aid to triage those in need for specialized diagnostic route besides having baseline cognitive data. Therefore we need to know its diagnostic test accuracy in this setting.

The MoCA shows good validity in multiple languages (*mocatest.org*), although moderately so in Dutch in a geriatric memory clinic setting (Thissen *et al.*, 2010). It is important to validate the MoCA in specific settings, as the selection of subjects with different characteristics may influence the test characteristics of a scale such as the MoCA (Rossetti *et al.*, 2011; Davis *et al.*, 2013, 2015). This is especially relevant in case-control study designs using community-based healthy controls, as this is not representative of the clinical reality (Davis *et al.*, 2013, 2015). The MoCA has not yet been validated in old age psychiatry settings, where patients are referred to with multidimensional causes for MCI (Ferri *et al.*, 2005) and to our knowledge our study is the first to do so. Differentiation between cognitive impairment as a consequence of a psychiatric disease and/or as a consequence of early stage dementia is complicated and may affect the test-characteristics of the

MoCA (Mitchell, 2009). According to the Cochrane review, "the MoCA may help identify people requiring specialist assessment and treatment for dementia" (Davis *et al.*, 2015).

We aim to validate the MoCA in this clinical setting following the standards for reporting diagnostic accuracy, STARD 2015 (Bossuyt *et al.*, 2015), recommendations by using a cross-sectional study design. The purpose of the present study is to test the criterion validity (i.e. can the MoCA predict a diagnose correctly) of the MoCA to detect MCI and early stage/mild dementia (MD) in an old age psychiatry cohort including referred but not cognitive impaired patients as primary comparisons. The reference standard consists of a multidisciplinary, consensus-based diagnosis in accordance with international criteria. The above cross-sectional design avoids the spectrum-bias of most case-control studies where the extremes of the spectrum of cognitive function were included (Davis *et al.*, 2013, 2015). To illustrate this effect, we present as a secondary outcome the MoCA results in a case-control design, using community-based healthy controls (HC) with normal cognitive aging as secondary comparisons.

3.2 Methods

3.2.1 Sample

This study was performed in an old age (60years +) psychiatry outpatient clinic in a large Dutch city (Utrecht) which offers services to the North-West side of the city and its rural surroundings (57.000 inhabitants of 60+ in the North-West). Between 2008 and 2018 all newly referred patients were eligible for this study. The inclusion criterion was the ability to give written informed consent. Therefore patients referred with severe dementia (Global Deterioration Scale (GDS) ≥6) (Reisberg *et al.*, 1982), Behavioral and Psychological Symptoms of Dementia (BPSD), or compulsory referrals were not included.

Participants were assessed by a multidisciplinary team, on all occasions including an old age psychiatrist and a trained psychiatric nurse practitioner. After referral, patients with an obvious cause of their cognitive complaints were excluded to resemble a clinical screening population: those with a diagnosis of severe mid-stage dementia (GDS ≥5), a recent history of substance abuse (<2 years), recent delirium (<6 months), or an acquired brain injury including CVA or TIA. In addition, patients with insufficient command of the Dutch language were excluded.

The secondary study compares the test properties of the MoCA with an unrealistic situation: a group of community-based HC, age 60+. They were recruited from acquaintances of patients or research assistants. Inclusion criteria were: no cognitive complaints and no risk

factors for cognitive dysfunction. Exclusion criteria were: acquired brain injury including CVA or TIA, substance abuse, recent delirium, recent treatment for psychiatric or neurologic diseases, and use of medication that can alter cognitive functioning. From potential HC showing signs of cognitive impairment during the interview or with a MoCA score below 25, consent was obtained to interview the next of kin (*n*=11), who were assessed with the Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCode) (De Jonghe, 1997). No potential HC had an IQCode higher than 3.5, which would indicate potential moderate cognitive impairment (De Jonghe, 1997) and would be an exclusion criterion.

The Committee for Research and Ethics of the institution approved this study (CWO-nr 1606). All participants gave their informed consent. Data available on request due to privacy/ethical restrictions.

3.2.2 Measurements

Initial assessment was performed by an old age psychiatrist, including a medical history obtained from the next of kin and relevant laboratory tests for cognitive impairment. During the diagnostic procedure the 15-item Geriatric depression Scale (GDS15) (Yesavage and Sheikh, 1986) and the Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) were collected. Investigation of Instrumental activities of daily living (IADL) was done by a psychiatric nurse practitioner on a home visit. When this initial assessment raised any suspicion of cognitive impairment, further assessment took place with a neuropsychological assessment (*n*=289) and, when applicable, CT/MRI imaging and Cerebrospinal Fluid (CSF) Analysis. The neuropsychological assessment, done by a neuropsychologist not aware of the MoCA score, was an extensive and comprehensive assessment including multiple tests in the domains of memory, attention, executive function, fluid intelligence and language capacities: (Full test: Dutch reading test for adults to estimate premorbid intelligence ("Nederlandse Leestest voor Volwassenen" NLV). Proverbs. Zung 12; Self-rating Depression scale (ZDS). Raven Coloured Progressive Matrices. Questionnaire for orientation and personal and non-personal episodic memories "Toutenburger Vragenlijst". Visual Association Test (VAT). 15 words imprinting and recall or recognition. Copying of Drawings; Meander of Luria, Complex figure of Rey, House, Cube, Greek cross. D-KEFS | Trail Making Test A and B (TMT). Hooper Visual Organization test (VOT-short version). Calculation, spelling and reading. Binet- Bobertag story. Fluency- test category (and letter). Groninger Intelligence test (GIT). Clock reading and writing. Subtest: Wechsler Adult intelligence scale; WAIS IV (Symbol substitution, Numerical series/ Digit Span, Agreements/ Similarities, Figures; Figure Weights). Wechsler Memory scale IV; WMS IV (numerical series). Behavioral Assessment of the Dysexecutive Syndrome (BADS; Key search test and Zoo-plan test).

The HC were interviewed and assessed by research assistants. The assessment was carried out in a single day and included the MoCA, the GDS15 and GAF.

3.2.3 Diagnostic test

All referred participants were assessed with a MoCA as soon as possible, within a maximum of 3 months from referral, by a trained research assistant or psychiatric nurse practitioner. This was independent from the diagnostic procedure. The MoCA was assessed during the feedback appointment of the initial assessment when the treatment-plan was presented. The treatment-plan included referral to our memory clinic for further assessment if there was doubt or suspicion of CI.

The MoCA consists of one page, covering the cognitive domains of executive function and visuospatial abilities, naming, sort term memory, attention and working memory, language, concentration, verbal abstraction, and orientation. It can be carried out within 10 minutes, with a maximum score of 30 indicating no errors were made. Scores were corrected for low education according to instructions, by adding one point to the total score of patients with 12 years of education or less. The original suggested cut-off for the diagnosis of CI was a score of (below) 26 (<26) (Nasreddine *et al.*, 2005).

3.2.4 Reference test

The reference test was the diagnosis determined at multidisciplinary team meetings, including an old age psychiatrist, neuropsychologist, and geriatrician.

The diagnoses of dementia and MCI were supported by a minimum of a neuropsychological assessment and laboratory tests. The diagnoses were made in consensus, and in accordance with the MCI criteria as proposed by an international consortium (Winblad *et al.*, 2004; Gauthier *et al.*, 2006), or the Dutch guideline on dementia (Nederlandse Vereniging voor Klinische Geriatrie, 2014). This guideline covers the criteria of -DSM IV for dementia, -NIA-AA / NINCDS-ADRDA for Alzheimer's disease (McKhann *et al.*, 2011), -NINDS-AIREN / AHA-ASA for Vascular dementia (Román *et al.*, 1993; Gorelick *et al.*, 2011), -Frontotemporal dementia (FTD) according The Lund and Manchester Groups (Neary *et al.*, 1994; Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011), and the Consensus for Dementia with Lewy Body (McKeith *et al.*, 2005). The MCI group included those with MCI due to psychiatric causes, in accordance with the international consensus (Winblad *et al.*, 2004; Gauthier *et al.*, 2006). No further differentiation of MCI was made in this study. The results of the MoCA were not used to diagnose MCI or Dementia.

Referred patients without suspicion of CI during initial assessment were followed up for a minimum of 2 years to compensate for not having a neuropsychological assessment. Patients who did not meet the aforementioned criteria for a diagnosis of dementia or MCI during follow-up were classified as No-Cognitive Impairment (NoCI). Patients who did meet the aforementioned criteria after the initial three months during follow-up were classified as inconclusive, to be cautious (*n*=3).

3.2.5 Statistical analyses

Results were compared within the referred patients with MD, MCI or NoCI, and between the groups Total Referred Patients (MD+MCI+NoCI) and HC, using the Statistical Package for the Social Sciences (SPSS, version 22; SPSS Inc., Chicago, IL); Chi2 test to compare Sex and education. ANOVA to compare age, GAF, GDS15, and MoCA scores followed with a Least Significant Difference (LSD) (and a Bonferroni not shown) post Hoc test. An ANCOVA with age as a covariate was run additionally.

Using Receiver Operating Characteristic (ROC) analysis, the Area Under the Curve (AUC) was calculated as a measure for the diagnostic accuracy of the MoCA. As the MoCA can be used to detect dementia in a clinical setting as well as to rule out cognitive impairment in a clinical setting, we calculated different ROC curves: 1. to detect dementia in a clinical setting. 2. to detect cognitive impairment (MD+MCI) in a clinical setting. 3. to detect MCI in in a subgroup of patients (MD excluded). To compare these analyses with previous case-control studies and to see the effect of bias, all analyses were repeated with HC.

Positive and negative predicting value (PPV,NPV) were calculated for the "optimal" cut-off scores as calculated by the Youden's J index. Cronbach's alpha was calculated for internal consistency of the MoCA.

3.3 Results

3.3.1 Study groups

Out of 2204 referrals, 1337 were not eligible for this study. 867 referred patients were assessed with a MoCA for this study (mean delay 21.5 days, 65% within 3 weeks of referral). After applying the exclusion criteria (figure 1), a group of 710 participants remained: 81 MD, 153 MCI, 459 referred patients with no MCI or dementia (NoCI), and 17 inconclusive. Mean time needed for diagnosing was 40.5 days for the NoCI and 60.8 for the CI. For the secondary outcome, 84 HC were included of a group of 96 potential healthy volunteers (flowchart figure 1). Two of them had an IQcode between 3.25-3.5 indicating minor decline over the past 10 years (Ehrensperger *et al.*, 2010). All others were in-between 3.0-3.25 indicating (almost) no decline.

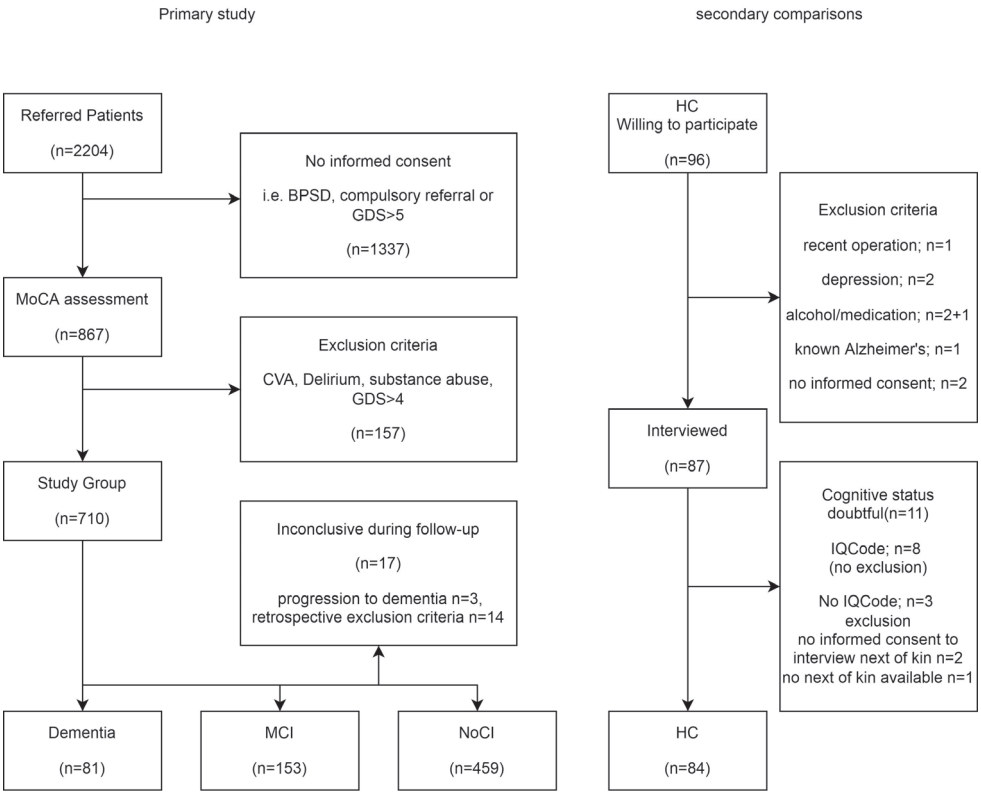


Figure 1. Flowchart Referred Patients and Healthy Controls

MCI: Mild Cognitive impairment NoCI: No Cognitive impairment; HC Healthy Controls;

GDS: Global Deteriorration Scale; IQCode: Informant Questionnaire on Cognitive Decline in the Elderly; BPSD: Behavioral and Psychological Symptoms of Dementia

3.3.2 Demographic findings

Within the referred patients, there was a significant difference in age (ANOVA F=26.0 *p*=0.000) between the diagnostic groups, as expected. There was no significant difference between sex (*p*=0.39) and education length (*p*=0.142). Disability, as measured by the GAF, showed an expected difference: MCI best and the demented and NoCI (as most of them were psychiatrically ill) the worst GAF-score (*p*=0.001). The GDS15 shows no significant differences between the referred groups.

As for the secondary outcome there were no significant differences in age, education and sex between the population of referred patients and the HC (table 1). The significant differences in GDS15 and GAF were as expected; the HC had significantly fewer depressive symptoms (GDS15-score) and better global functioning (GAF-score).

Table 1: key demographic and clinical characteristics

	Clinical population	Primary outcome			Secondary outcome	
	Total Referred (a)	Dementia (b)	MCI (c)	NoCI (d)	Healthy Controls (e)	Statistical difference p<0.001
Variable / *n*	**693**	**81**	**153**	**459**	**84**	
Age	72.5	77.3	73.9	71.3	73.5	
(SD)	(7.8)	(7,5)	(8.0)	(7.3)	(7.8)	b>c>d
range	53-94	59-94	53-93	58-92	60-91	
Education <12 (%)	47	52	53	43	45	No sig.
Sex F (%)	62	63	57	63	59	No sig.
GAF	53.3	52	57	52	84	a<e
(SD)	(12.3)	(10.2)	(12.8)	(12.4)	(5.9)	b,d<c
GDS15	8.4	6.6	7.7	8.6	1.3	a>e
(SD)	(4.3)	(4.9)	(4.7)	(4,3)	(2.0)	
MoCA	22.1	16.5	20.9	23.5	26.5	a<e
(SD)	(4.7)	(4.0)	(3.8)	(4.2)	(2.6)	b<c<d
range	3-30	5-26	3-28	3-30	20-30	

Education and sex were compared between b,c,d and between a,e with a Chi2 test.

Groups b,c,d and were compared with ANOVA, Groups a,e were compared with t-test.

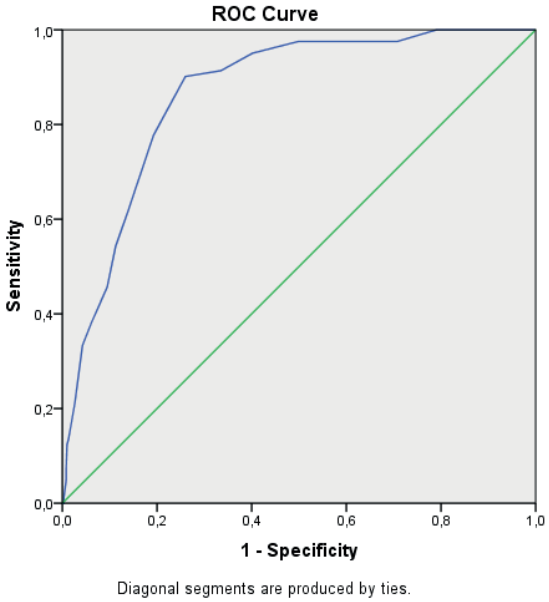
MCI: Mild Cognitive Impairment; NoCI: No Cognitive Impairment; GAF: Global Assessment of Functioning; GDS15: Geriatric Depression Scale 15 question version; MoCA: Montreal Cognitive Assessment.

3.3.3 MoCA outcome

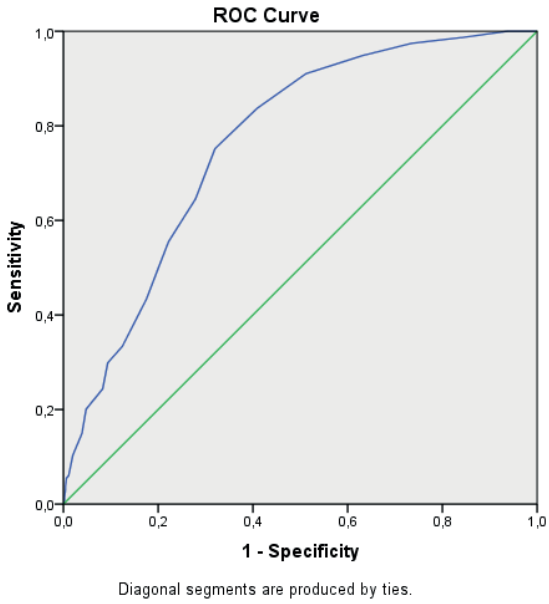
The mean MoCA-scores differed significantly between groups; the differences in average MoCA scores between the individual referred groups were significant (p=0.000), as well as those for the secondary outcome between combined total referred group and the HC (p=0.000). The standard deviations (MCI towards NoCI) and range (all groups) of the referred groups did overlap, and showed a wide distribution (table 1). The internal consistency of the MoCA, as expressed by the Cronbachs alpha on the standardized items (0.761), was good. All 12 items of the MoCA contribute to a positive Cronbachs alpha, as no item "if item deleted" gives a higher outcome (0.708- 0.737).

The results of the ROC analysis, for clinical situations, are shown in figure 2: a) Dementia versus No-Dementia (MCI + NoCI) and b) Cognitive Impairment (CI= MD + MCI) versus NoCI. Table 2 displays the AUCs of these and additional analyses, as well as their sensitivity and specificity at the literature-recommended cut-off scores of 26 and 21. All AUCs were significantly different from 0.5 (no diagnostic accuracy), p<0.001. The AUCs with HC as secondary comparison ranged between 0.90 and 0.98, an excellent accuracy. The MoCA performed less well in a clinical setting, with AUCs between 0.70-0.87.

Figure 2 a, b: Results of ROC Analysis



a. **Dementia (*n*=81) versus No-Dementia (MCI + NoCI *n*=612)**



b. **Cognitive Impairment (Dem + MCI *n*=234) versus No-Cognitive Impairment (*n*=459)**

For the original suggested cut-off score of 26 to discriminate MCI from HC the sensitivity and specificity are 94% and 73%, respectively (in the original article 90% and 87%)(Nasreddine *et al.*, 2005). Using the same cut-off score in a realistic setting (i.e. discriminating against referred NoCI) leads to a drop in specificity to 37%. The clinical situation of detecting CI (MD+MCI) below this cut-off had a sensitivity of 95%.

Table 2: The effect of using HC instead of NoCI as comparisons on Area Under the Curve between variations of groups and their sensitivity and specificity at cut-off scores 26 and 21, often used in literature.

groups			**AUC**	**SE**	**CutOff <26**		**CutOff <21**	
					Sens	**Spec**	**Sens**	**Spec**
Dem	vs	NoDem	.865	.018	.975	.737	.901	.740
Dem	vs	HC	.983	.007	.975	.726	.901	.988
Dem	vs	MCI	.810	.029	.975	.065	.901	.627
CI	vs	NoCI	.765	.018	.949	.368	.556	.778
CI	vs	HC	.925	.016	.949	.726	.556	.988
MCI	vs	NoCI	.702	.022	.935	.368	.373	.778
MCI	vs	HC	.894	.022	.935	.726	.373	.988

Dem: Dementia (*n*=81); NoDem: No Dementia (MCI + NoCI; *n*=612); MCI: Mild Cognitive impairment (*n*=153); NoCI: Referred patients no Cognitive Impairment (*n*=459); HC: Healthy Controls (*n*=84); CI; Cognitive Impairment (Dem + MCI; *n*=234). AUC: Area Under the Curve. SE: standard error. Sens: sensitivity. Spec: specificity.

A cut-off score for diagnosing dementia is still under debate, but is often set around 21 (Thissen *et al.*, 2010; Waldron-Perrine and Axelrod, 2012; Davis *et al.*, 2015), which in our study results in a sensitivity of 90%. The specificity dropped from 99% using Dementia vs HC, to 74% in a clinical setting (Dementia vs MCI+NoCI), and 63% for Dementia vs MCI. To find the "best" cut-off score for our population, the specificity and sensitivity were calculated for different scores of the MoCA (table 3).

Table 3: Sensitivity and Specificity at MoCA scores from 18 through 28

Cut-off value†	**Sensitivity**	**Specificity**			
		MCI+NoCI No Dementia	**MCI**	**NoCI**	**HC** (secondary comparison)
Dementia					
18	54%	89%	83%	91%	100%
19	62%	86%	82%	88%	100%
20	78%	81%	75%	83%	100%
21	90%	74%	63%	78%	99%
22	91%	67%	50%	73%	93%
23	95%	60%	35%	68%	89%
24	98%	50%	24%	59%	81%
25	98%	40%	12%	49%	79%
26	98%	29%	7%	37%	73%
CI (Dem+MCI)					
18	30%			91%	100%
19	33%			88%	100%
20	43%			83%	100%
21	56%			78%	99%
22	65%			73%	93%
23	75%			68%	89%
24	84%			59%	81%
25	91%			49%	79%
26	95%			37%	73%
MCI					
18	17%			91%	100%
19	18%			88%	100%
20	25%			83%	100%
21	37%			78%	99%
22	50%			73%	93%
23	65%			68%	89%
24	77%			59%	81%
25	88%			49%	79%
26	94%			37%	73%

†(MoCA-D below score)

Dem: Dementia (*n*=81); MCI: Mild Cognitive impairment (*n*=153); NoCI: Referred patients no Cognitive Impairment (*n*=459); HC: Healthy Controls (*n*=84); CI; Cognitive Impairment (Dem + MCI; *n*=234).

The "optimum" cut-off scores against NoCI as calculated by the Younden index were <25 for detecting MCI ,sensitivity 88% (95%CI:81-92), specificity 49% (95%CI:44-53); <23 for CI, sensitivity 75% (95%CI:69-81), specificity 68% (95%CI:63-72); and <21 for MD, sensitivity 90% (95%CI:81-95), specificity 78% (95%CI:74-81) and comparable to literature (Lee *et al.*, 2008; Memõria *et al.*, 2013; Gil *et al.*, 2015; Carson, Leach and Murphy, 2018; Pugh *et al.*, 2018).

The Positive Predictive value (PPV) and Negative Predictive value (NPV) were calculated (table 4) for the two scores with the highest computed Younden index. The PPV and the NPV show different results. The PPV was low in almost all situations whereas the NPV was high in all situations. Using a cut-off of <21 for dementia results in 31% of a positive MoCA having MD and 98% of a negative test having no MD. For detecting MCI at a cut-off of <26; 33% has indeed MCI when the MoCA is positive and 94% above this threshold will not have MCI.

Table 4: Positive and Negative predictive values of cut-off scores with the highest Younden index

Cut-off value†	**No Dem**		**MCI**		**NoCI**	
	PPV %	NPV %	PPV %	NPV %	PPV %	NPV %
Dem						
20	35	97	62	87	44	96
95%CI	(28-42)	(94-98)	(52-72)	(79-92)	(36-53)	(93-97)
21	31	98	56	92	42	98
95%CI	(26-38)	(96-99)	(47-65)	(84-96)	(34-49)	(96-99)
CI						
23					54	84
95%CI					(49-60)	(80-88)
24					51	88
95%CI					(46-56)	(83-91)
MCI						
25					36	92
95%CI					(31-41)	(88-95)
26					33	94
95%CI					(29-38)	(90-97)

† (MoCA-D below score)

Dem: Dementia (*n*=81); MCI: Mild Cognitive impairment (*n*=153); NoCI: Referred patients no Cognitive Impairment (*n*=459); HC: Healthy Controls (*n*=84); CI; Cognitive Impairment (Dem + MCI; *n*=234). PPV: Positive Predictive Value. NPV: Negative Predictive Value. 95%CI: 95% Confidence Intervals.

3.4 Discussion

In this cross-sectional study, patients with dementia were significant older than those without. There were more females in each group, which is representative of the population referred to old age psychiatry. Age has been shown to be of influence (Rossetti *et al.*, 2011; Freitas *et al.*, 2012; Larouche *et al.*, 2016; Carson, Leach and Murphy, 2018), as MoCA scores decline with aging and can alter the (interpretation of) results. However, age has little unique variance and a correlation of less than 10% (Waldron-Perrine and Axelrod, 2012). An additional ANCOVA sensitivity analysis with age as a covariate still showed significant differences in MoCA scores between the different diagnostic groups in our study.

The GDS15, a geriatric depression scale, revealed no differences between the referred groups. This finding underscores again the necessity to be cautious when using a screening tool like the GDS15 in attempting to differentiate between or detect psychiatric causes of cognitive complaints (De Craen, Heeren and Gussekloo, 2003).

Our study reproduced the significantly different mean MoCA scores reported in previous literature (*mocatest.org*, no date; Davis *et al.*, 2015; O'Caoimh, Timmons and Molloy, 2016; Carson, Leach and Murphy, 2018). Our secondary outcome, differentiating patients with MD or MCI from HC, shows comparable properties reported in previous case-control studies (*mocatest.org*, no date; Gil *et al.*, 2015). But to avoid this spectrum-bias, we studied the MoCA in a cohort of patients referred to old age psychiatry, which more accurately represents the clinical reality. This is illustrated in table 3, where the AUC and specificity drop when the comparison is realistic (NoCI as comparisons) and not fictive (HC as comparisons). One can argue that this bias we underscore, by adding HC, is well-known and its effect on the AUC shown before (O'Caoimh, Timmons and Molloy, 2016). Apparently it is still important to stress out the effect it has on optimum cutoff scores as the case-control study design is still the majority of the MoCA validation studies(Nasreddine *et al.*, 2005; Davis *et al.*, 2015). Clinicians should be careful to use cutoffs based on those studies. Twenty-seven percent of the HC had a MoCA score below 26, compared to 63% of the referred NoCI. The MoCA scores of our NoCI patients match with that of a longitudinal, population based study (n=2653; mean MoCA 23.36, 64% specificity <26) indicating we have a realistic comparison group (Rossetti *et al.*, 2011). Even though there was a wide range of MoCA scores in our group, this occurred in a clinical setting and can be explained by the following.

False negative results were found in cases of high educational and/or professional levels or Frontotemporal Dementia (FTD) in the dementia group. False positive results occurred due to a lack of motivation and/or attention in depressed, manic or psychotic patients,

with or without MCI. One may argue the latter should have been diagnosed with MCI due to their psychiatric conditions. However, it was the clinical opinion of the team, after IADL investigation, that their presentation was not persistent and did not justify a diagnosis of MCI, as the MoCA score was not taken into account.

There is a risk, including in this study, of a subjective decision whether MCI is diagnosed or not when a psychiatric disorder explains its etiology, despite the criteria for MCI being met. We minimized this by including a Neuropsychological assessment during the diagnostic work-up when there was suspicion of persistent impaired cognitive functioning. In the future the MoCA would make it easier and more objective to select these possible MCIs and identify those in need of a further work-up.

False positives (i.e. a low MoCA score) due to unrecognized neurodegenerative MCI can be excluded in our study, as progression to any DSM IV diagnosis of cognitive impairment was monitored with a mean follow-up of 3.5 years. This study shows it is safe to use a threshold of ≥26 to indicate normal-cognition (95% sensitivity for CI), taking specific situations, like a university degree or FTD, into account. While the MoCA detects most MD (<21; 90% sensitivity) and MCI (<26; 94% sensitivity) below these cut-off scores, making it fit for screening, it is not suitable for diagnosing MD or MCI in our study population, as the PPV for MD and MCI are still only fair (31% and 33% PPV respectively). The proportion of referred psychiatric patients scoring below these cut-off scores is too high for diagnostic purposes (22% and 63% of NoCI, respectively).

The MoCA is suitable for excluding dementia (≥21; NPV 92-98%) and MCI (≥26; NPV 94%), if used to assess patients referred to an old age psychiatry setting. This, combined with the high sensitivity at these cut-offs, makes the MoCA a useful screening tool.

In the case of a positive test result, further work-up is usually necessary; the absolute amount of false-positives is substantial, since the majority of referred patients do not suffer from mild dementia.

Using our study cohort as an example, applying a MoCA cut-off of <21 to screen 100 referred patients would lead to 33 patients receiving specialized diagnostic tests, of whom 14.7 would be NoCI, 8.2 MCI, and 10.5 correctly identified MD. One patient (1.15) with MD would not be detected using this cut-off score. This confirms that screening comes with its price, also in old age psychiatry.

We recommend further research to find methods that increase the specificity and improve selection of those in need of a specialized diagnostic pathway. The aforementioned

weaknesses of our study – unrealistic scattering and seemingly missed CI diagnoses – would in practice be interpreted as part of a larger clinical picture; incongruous results would be reconsidered if these MoCAs are clinically relevant or correct, or considered as CI. This would increase the specificity of the MoCA. Further research should focus on the suspected CI referrals only and investigate if a MoCA reassessment after recovery from serious psychiatric episodes can lower the false positive rate. Another limitation is that we did not gave all the comparisons the same full diagnostic assessment due to practicality and resource constraints. Because adding the HC was mainly to underscore the spectrum-bias effect, this is to our opinion acceptable.

The NoCI that were not suspected of CI, hence didn't got a full diagnostic work-up, were followed for at least 2 years to compensate for this limitation. The NoCI that were suspected of CI did get the same full diagnostic assessment. Excluding the GDS ≥5 and BPSD could be seen as selection-bias and a limitation. To our opinion avoiding the extremes of the spectrum is a strength of our study. The clinical reality is that the obvious demented will not be screened whether they need a specialized diagnostic route. But including their low MoCA scores in the study would bias the results.

3.5 Conclusion

This study shows that validating the MoCA in a biased setting, i.e against healthy controls, overestimates specificity. Our findings are in line with the literature, where lower cut-off scores are repeatedly suggested (Lee *et al.*, 2008; Rossetti *et al.*, 2011; Waldron-Perrine and Axelrod, 2012; Davis *et al.*, 2015; Gil *et al.*, 2015; O'Caoimh, Timmons and Molloy, 2016; Carson, Leach and Murphy, 2018; Pugh *et al.*, 2018) to tackle this problem.

Taking the above results into account, one can conclude that the MoCA can be useful in an old age psychiatric setting to confirm normal cognitive functioning and to identify those who are in need for a specialized diagnostic pathway. However, further research is necessary to minimize the number of false positives in the latter group.

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CHAPTER

Clinical value of the Montreal Cognitive Assessment (MoCA) in patients suspected of cognitive impairment in old age psychiatry. Using the MoCA for triaging to a memory clinic

4

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Cognitive Neuropsychiatry 2021 Jan;26(1):1-17

doi: 10.1080/13546805.2020.1850434

ABSTRACT

Objectives:

Diagnostic pathways are limited. A validated instrument that can triage patients when they are suspected of mild dementia (MD) is necessary to optimize referrals.

Methods:

The MoCA is validated for identifying MD and mild cognitive impairment (MCI) in a cohort of patients suspected of cognitive impairment (CI) after initial assessment in old age psychiatry. The reference standard was the consensus-based diagnoses for MD and MCI, adhering to the international criteria and using suspected patients that followed the same diagnostic route, but without CI, as comparisons (SNoCI).

Results:

The mean MoCA scores differ significantly between the groups: 24(SE:.59) in SNoCI, 21(SE:.31) in MCI and 17(SE:.45) in MD ($p<0.05$). The AUC of MD against non-demented (MCI+SNoCI) was 0.83 (95%CI: 0.78-0.88) resulting in 90% sensitivity, 65% specificity, 50% PPV and 94% NPV at a 'best' cutoff of <21 according the Youden index and respectively 0.77 (95%CI: 0.69-0.85), 56%, 73%, 90%, 28% for CI (MD+MCI) against SNoCI at <21.

Conclusion:

90% of individuals with a MoCA of <21 will have CI (MD+MCI), while 94% with a MoCA of ≥21 will not have dementia. The MoCA can reduce referrals substantially (50%) by selecting who doesn't need further work up in a memory clinic, even if they were suspected of CI after initial assessment.

4.1 Introduction

Diagnosing, as well as the guidance and treatment of dementia, including Behavioral and Psychological Symptoms of Dementia (BPSD), is often done in old age psychiatry which, at least in the Netherlands, make up to 25% of all memory clinics (Verhey, et.al 2010). Here, patients with a wide variety of etiologies of possible cognitive impairment (CI) are presented- including major depressive- , schizophrenic- and bipolar- disorders. More referrals to memory clinics and old age psychiatry should be expected due to demographic reasons and more awareness of CI (Alzheimer's disease International, 2016) alongside the trend of earlier assessment with less pronounced symptoms (Grimmer et al., 2015). A validated short tool to assess patients that are suspected of CI to objectify the complaints, before further referral, is necessary to triage who is indeed in need of an elaborate diagnostic investigation for dementia. This could help to relieve the pressure on diagnostic pathways (Alzheimer's disease International, 2016; Davis et al., 2015), which are costly and scarce in most countries (Alzheimer's Disease International, 2018). Especially as doctors without an objective test rather refer too early than too late to avoid a missed diagnose and this raises the false positive referrals.

According to the Cochrane review, 'the MoCA may help identify people requiring specialist assessment and treatment for dementia' (Davis et al., 2015, p.5). General practitioners in the Netherlands are advised to use the Montreal Cognitive Assessment (MoCA) especially for patients with 'possible CI' but less so for 'not likely' or 'likely' CI patients (Janssen et al., 2017). Screening older patients with the MoCA is often recommended as subjective cognitive complaints agree poorly with objective cognitive deficit (Pendlebury et al., 2015) but results in too many false positives in old age psychiatry (Dautzenberg et al., 2020). Using an objective test (the MoCA) only for suspected patients concurs with the above need for triaging possible impaired patients and is especially welcome in old age psychiatry, as the (subjective) cognitive complaints are numerous due to age (60+), psychiatric comorbidity (including psychotropic medication) causing CI next to CI as a primary reason for referral.

The MoCA is a widely used short screening tool for mild cognitive impairment (MCI) and mild dementia (MD) (Alzheimer's disease International, 2016; Davis et al., 2013; Nasreddine et al., 2005), validated in multiple settings and languages (*Mocatest.Org*). However, many of these studies were designed with a case-control set-up using healthy, community-based individuals as controls (Davis et al., 2015), which can result in spectrum-bias (Dautzenberg et al., 2020; Davis et al., 2015; Noel-Storr et al., 2014), overestimating specificity. In literature, lower cutoff scores are repeatedly suggested for clinical use,

especially with MD (Carson et al., 2018; Davis et al., 2015; Elkana et al., 2020; Gil et al., 2015; Larner, 2012; Lee et al., 2008; O'Caoimh et al., 2016; Pugh et al., 2018; Rossetti et al., 2011; Waldron-Perrine & Axelrod, 2012).

A test needs to be validated in its corresponding clinical setting (Noel-Storr et al., 2014), as the prevalence of the index disorder and the clinical setting influences results of the validation of tests.

Our aim was to test the criterion validity of the MoCA for MD after initial assessment in old age psychiatry, in order to examine the added value of the MoCA for triaging patients for further specialized work-up. These patients were suspected of cognitive problems on clinical judgment without a cognitive test. To our knowledge, this is the first time the MoCA has been validated for this use in old age psychiatry. Our reference standard consisted of a consensus-based diagnosis adhering to international criteria resulting in patient groups with MCI, MD, and patients suspected of MCI/MD -but ruled out of having cognitive impairment (SNoCI) from the same cohort.

4.2 Methods

4.2.1 Study samples

All newly referred patients for diagnostic purposes from the North-West part of Utrecht (the Netherlands) to our old age psychiatry memory clinic between 2008 and 2018 were eligible for the study if they were capable of giving written informed consent. This clinic offers services to 57.000 inhabitants of 60+ in the North-West side of the city and its rural surroundings and is one out of four memory clinics in the bigger metropolitan area. Therefore, patients with severe dementia (Global Deterioration Scale (GDS) ≥6) (Reisberg et al., 1982) or Behavioral and Psychological Symptoms of Dementia (BPSD) as a reason for referral, as well as compulsory referrals, were not eligible (*n*=1337). Exclusion criteria included patients with a diagnosis of severe mid-stage dementia (GDS ≥5) to prevent inclusion of the extreme of the spectrum – as this could lead to spectrum bias (Noel-Storr et al., 2014) –, or other obvious causes of CI, such as; a recent history of substance abuse (<2 years), a delirium (<6 months), or an acquired brain injury including CVA or TIA (*n*=174). Only those patients that were referred to our memory clinic after the initial assessment at our old age psychiatric service were included (*n*=292) (figure 1).

All of these patients followed a comprehensive cognitive diagnostic route for CI using a consensus based diagnosis following international criteria as a reference standard with a

neuropsychological assessment, and when applicable CT/MRI- imaging and Cerebrospinal Fluid (CSF) Analysis (Dautzenberg et al., 2020; Nederlandse Vereniging voor Klinische Geriatrie, 2014). They were classified as MD, MCI or SNoCI. We further differentiated these groups by the most likely cause by DSM IV (American Psychiatric Association, 2000) and clustered the neurodegenerative (MCI-N.D.) and psychiatric causes (MCI-Psy) for the MCI-group. We did not differentiate the MCI into non/amnestic uni- or multi-domain.

The comparisons consisted of SNoCI patients from this cohort. Therefore avoiding spectrum-bias due to healthy controls and avoiding selection-bias by including naturalistic possible etiologies to comply with the Standards for Reporting of Diagnostic Accuracy dementia (STARD-Dem) (Noel-Storr et al., 2014).

The Committee for Research and Ethics of the institution approved this study (CWO-nr 1606).

All participants gave their informed consent. Data are available on request.

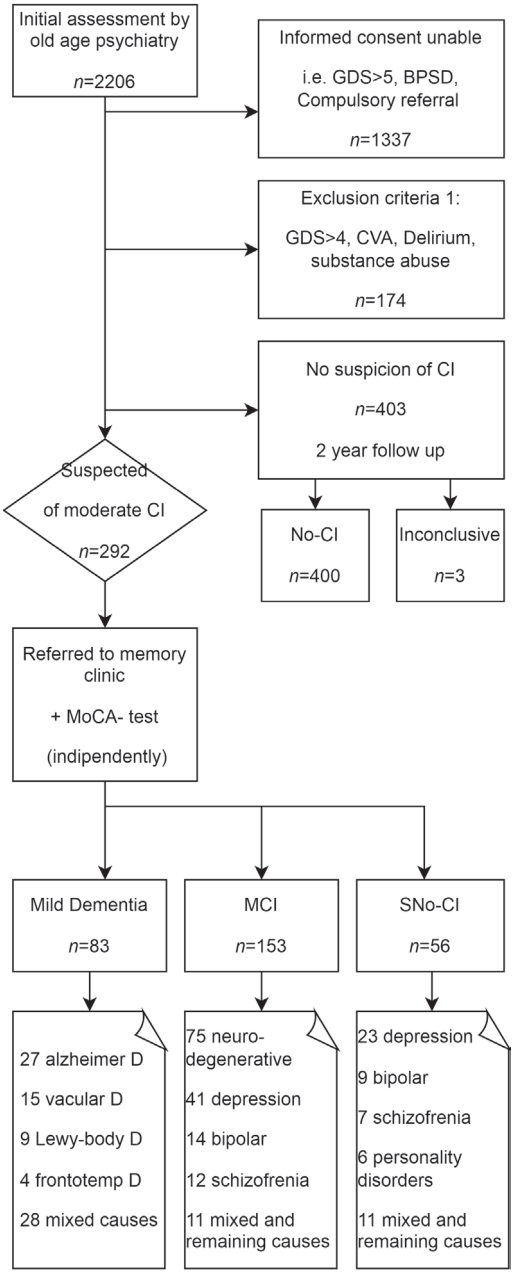


Figure 1. Flowchart Suspected Patients

CI: Cognitive Impairment; MCI: Mild Cognitive Impairment; No-CI: No Cognitive Impairment; SNo-CI: Suspected but No Cognitive Impairment.

GDS: Global Deterioration Scale; BPSD: Behavioral and Psychological Symptoms of Dementia

4.2.2 Measurements

Initial assessment

This was completed by an old age psychiatrist and included; a laboratory test (table 1), medical and functional history from a next of kin and an investigation of Instrumental Activities of Daily Living (IADL) completed by a psychiatric nurse practitioner during a home visit. The 15-item Geriatric depression Scale (GDS15) (Yesavage & Sheikh, 1986) and the Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) were also taken during this time. If this resulted in suspicion or doubt of CI, the patients were referred to the memory clinic.

Table 1. Details of the diagnostic tests

The Neuropsychological assessment consisted of the following assessments:	
Full Test	**Subtest**
Dutch reading test for adults to estimate premorbid intelligence ("Nederlandse Leestest voor Volwassenen" NLV), proverbs, Zung 12; Self-rating Depression scale (ZDS), Raven Coloured Progressive Matrices Questionnaire for orientation and personal and non-personal episodic memories "Toutenburger Vragenlijst" Visual Association Test (VAT) 15 words imprinting and recall or recognition Copying of Drawings; Meander of Luria, Complex figure of Rey, House, Cube, Greek cross. D-KEFS | Trail Making Test A and B (TMT) Hooper Visual Organization test (VOT-short version) Calculation, spelling and reading Binet- Bobertag story Fluency- test category (and letter) Groninger Intelligence test (GIT) Clock reading and writing	Wechsler Adult Intelligence Scale; WAIS IV (Symbol substitution, Numerical series/ Digit Span, Agreements/ Similarities, Figures; Figure Weights), Wechsler Memory scale IV; WMS IV (numerical series) Behavioral Assessment of the Dysexecutive Syndrome (BADS; Key search test and Zoo-plan test),

Laboratory tests consisted of:

Full Blood count; Erythrocyte sedimentation rate (ESR); Potassium (K); Sodium (Na); Creatinine (creat); Calcium (Ca); Urea (Ur); Aspartate transaminase (AST); Alanine transaminase (ALT); Gamma-glutamyltransferase (yGT); Alkaline phosphatase (ALP); Glucose non-fasting (Glu); Thyroid Stimulating Hormone (TSH); Albumin; Vitamin B1,B12,D; Folic acid; Albumin (Alb); Total protein; Magnesium (Mg); Syphilis

Diagnostic test

All of the participants were assessed with a MoCA as soon as possible but within 3 months of initial assessment. This was done by a trained psychiatric nurse practitioner at the old age psychiatry clinic independent of the decision to refer to the memory clinic.

The MoCA consists of one page that covers the cognitive domains of executive function and; visuospatial abilities, naming, short term memory, attention and working memory,

language, concentration, verbal abstraction and orientation. It can be applied within 10 minutes and the maximum score is 30 which indicates no errors were made. Correction for low education effects were made, according to the instructions, by adding one point to the total of patients with 12 years of education or less. Suggested cutoff for the diagnosis of dementia was a score of 21 (<21), for MCI <26. These cutoffs gave the best Youden index for this population (Dautzenberg et al., 2020).

Reference test

The reference test was the diagnosis determined at multidisciplinary meetings, these meetings included an old age psychiatrist, a neuropsychologist and a geriatrician. The diagnosis of MD, MCI or SNoCI was supported with (at least) a 4 hour neuropsychological assessment. This included multiple tests in the domains of memory, attention, executive function, fluid intelligence and language capacities (table 1). The diagnoses were made in consensus and in accordance with the DSM IV (American Psychiatric Association, 2000), the MCI criteria as proposed by an international consortium (Gauthier, et al., 2006; Winblad et al., 2004), or the Dutch guideline on dementia (Nederlandse Vereniging voor Klinische Geriatrie, 2014). This guideline covers the criteria of -DSM IV for dementia, -NIA-AA / NINCDS-ADRDA for Alzheimer's disease (McKhann et al., 2011), -NINDS-AIREN / AHA-ASA for Vascular dementia (Gorelick et al., 2011; Román et al., 1993), -Frontotemporal dementia (FTD) according The Lund and Manchester Groups (Gorno-Tempini et al., 2011; Neary et al., 1994), and the Consensus for Dementia with Lewy Body (DLB) (McKeith et al., 2005). The results of the MoCA were not used to diagnose MCI or Dementia.

4.2.3 Statistical analyses

Demographic and clinical variables were compared within patients suspected of MD, MCI or SNoCI using Statistical Package for the Social Sciences (SPSS, version 22; SPSS Inc., Chicago, IL); Chi2 test to compare Sex and education. ANOVA to compare age, GAF, GDS15, and MoCA scores followed with a Least Significant Difference (LSD) post Hoc test. Using Receiver Operating Characteristic (ROC), analysis of the Area Under the Curve (AUC) was calculated as a measure for the diagnostic accuracy of the MoCA.

We calculated three different ROC curves, as the MoCA can be used for different tasks: 1. to find dementia (MD versus MCI+SNoCI); 2. to rule out Cognitive Impairment (MD+MCI versus SNoCI); and; 3. to detect MCI (MCI versus SNoCI) (as CI is a multidimensional state, one may also want to identify who is at risk for developing dementia by focusing on MCI).

Positive and negative predictive values (PPV, NPV) were calculated for the 'optimal' cutoff scores as calculated by the Youden's J index. Boxplots were calculated to understand the distribution of the total MoCA scores for the main diagnostic groups and for their underlying DSM IV diagnosis to further explore the origin of the false positive (FP) and false negative (FN) results.

4.3 Results

4.3.1 Study groups

Out of 2206 patients referred to the old age psychiatry clinic, 1337 were deemed ineligible for this study as they were not capable of giving informed consent. The exclusion criteria listed above were applied to exclude the extremes of the spectrum (n=174). Of the remaining 695 patients, 292 were suspected of CI and underwent further assessment at our memory clinic. All were included in calculating the diagnostic accuracy of the MoCA in this setting (figure 1). This resulted in 83 MD, 153 MCI and 56 SNoCI patients. The different underlying disorders are shown in the flowchart (figure 1).The average time between the initial assessment and the assessment of the MoCA was 21.5 days and 60.8 days for diagnosing CI at the memory clinic.

Table 2. key demographic and clinical characteristics

	Dementia (a)	**MCI (b)**	**SNoCI (c)**	**Total Referred (d)**	Statistic difference p<0.05
Variable / *n*	**83**	**153**	**56**	**292**	
Age	77.3	73.9	71.0	74.3	
(SD)	(7.5)	(8.0)	(7.2)	(8.0)	a>b>c
range	59-94	53-93	58-85	53-94	
Education <12 (%)	52	53	44	51	No sig.
Sex F (%)	63	57	56	59	No sig.
GAF	52	57	54	55	a<b
(SD)	(10.2)	(12.8)	(11.4)	(12.0)	
GDS15	6.6	7.7	8.9	8.4	No sig.
(SD)	(4.9)	(4.7)	(4,3)	(4.5)	
MoCA	16.7	20.9	23.9	20.3	
(SD)	(4.1)	(3.8)	(4.3)	(4.7)	a<b<c
range	5-26	3-28	12-30	3-30	

Education and sex were compared between a,b,c, with a Chi2 test.

Groups a,b,c and were compared with ANOVA.

MCI: Mild Cognitive Impairment; SNoCI: Suspected but No Cognitive Impairment; GAF: Global Assessment of Functioning;

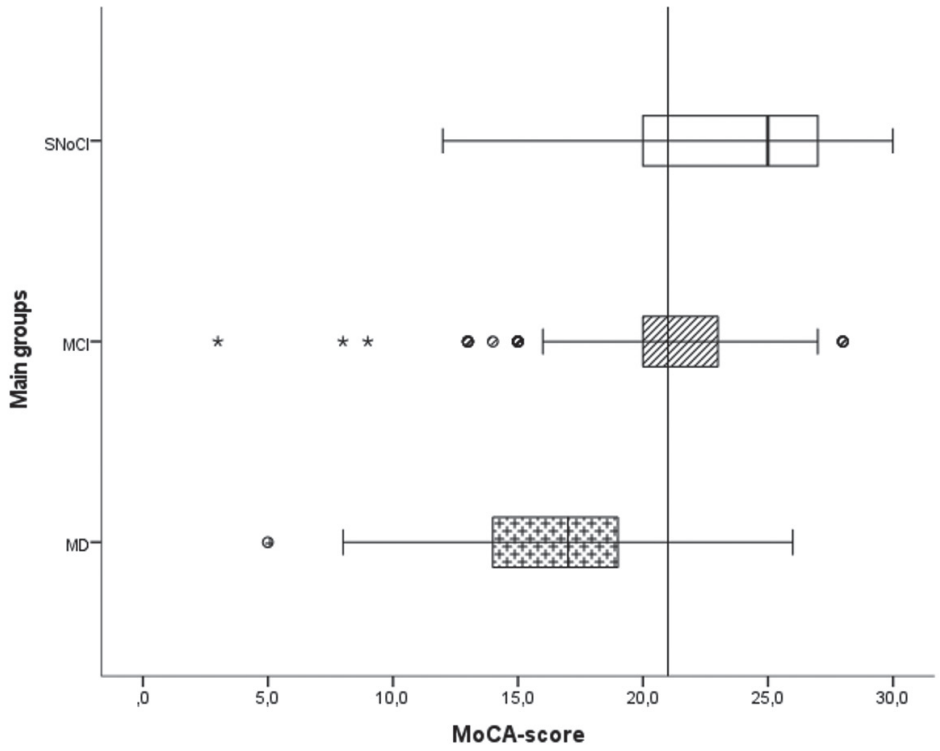
GDS15: Geriatric Depression Scale 15 question version; MoCA: Montreal Cognitive Assessment.

4.3.2 Demographic and clinical findings

The key demographic and clinical characteristics of the study group are displayed in table 2.

The male-female ratio did not differ significantly between the groups. The significant differences in age were representative of the demographics of an old age psychiatry setting. The GAF score was the highest in the MCI group, as they were the least afflicted. Of the MCI patients 50% (n=75) had no psychiatric disorder besides the MCI.

As would be expected, the mean MoCA scores differed significantly ($p<0.05$) between the three groups: a mean of 24 (SE:.59) in SNoCI, 21 (SE:.31) in MCI and 17 (SE:.45) in the MD group (table 2). The distribution of the MoCA scores for the main diagnostic groups and their DSM IV etiologies (including the prevalence) are presented in figure 2.



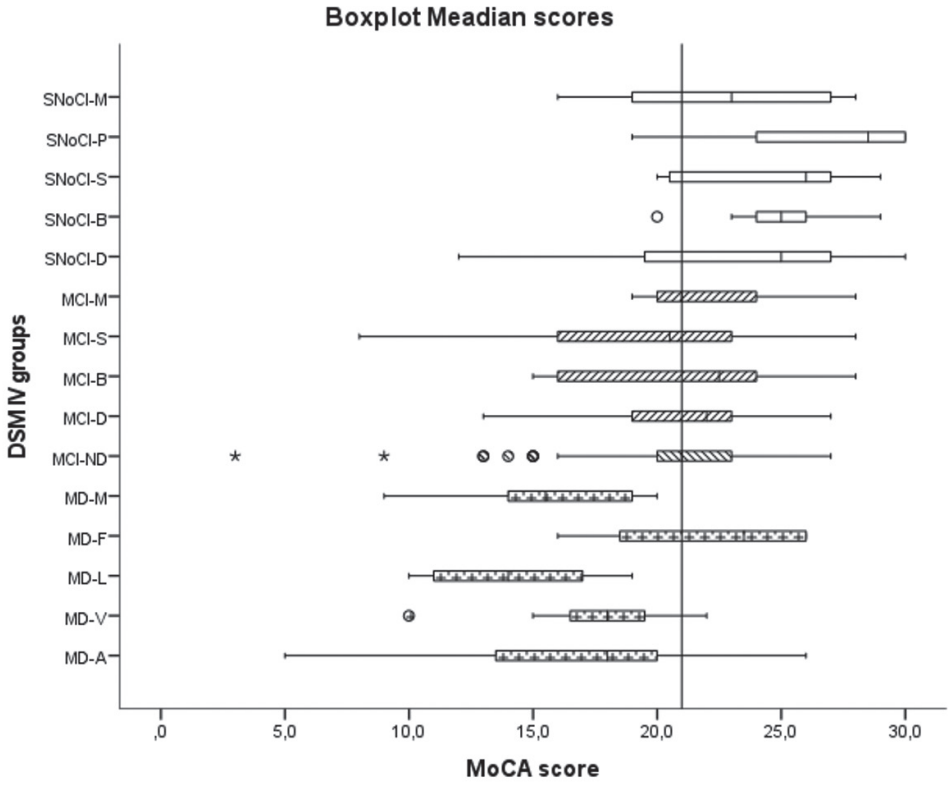


Figure 2. Boxplot Median scores

Left part Main groups:

SNoCI: suspected but No Cognitive Impairment (*n*=56: white boxes). MCI: Mild Cognitive impairment (*n*=153: striped boxes). MD: Mild Dementia (*n*=83:cross boxes).

Right part DSM IV groups:

SNoCI-D: NoCI and depression (*n*=23). SNoCI-B: SNoCI and Bipolar disorder (*n*=9). SNoCI-S: SNoCI and schizophrenia (*n*=7). SNoCI-P: SNoCI and personality disorders (*n*=6). SNoCI-M: SNoCI and remaining or mixed causes (*n*=11).

MCI-ND:MCI due to neurodegenerative process (*n*=75). MCI-D: MCI and depression (*n*=41). MCI-B: MCI and bipolar disorder (*n*=14). MCI-S: MCI and schizophrenia (*n*=12). MCI-M: MCI remaining or mixed causes including *Not otherwise specified* (*n*=11).

MD-A: Alzheimer's Dementia (*n*=27). MD-V: Vascular Dementia (*n*=15). MD-L: Dementia Lewy-body (*n*=9). MD-F: Frontotemporal Dementia (*n*=4). MD-M; Dementia mixed causes and *Not otherwise specified* (*n*=28).

Star outlier = 3.0×IQR (Interquartile range)

Point outlier = 1.5×IQR (Interquartile range)

4.3.3 ROC analysis

The ROC curves of the three different comparisons are presented in figure 3a,b,c and their AUC in table 3 along with the sensitivity, specificity, PPV and NPV of the MoCA scores of <26 (original cutoff) and <21 (best Youden score for MD). The sensitivity and specificity for the cutoffs from 26 through 18 are presented in table 4.

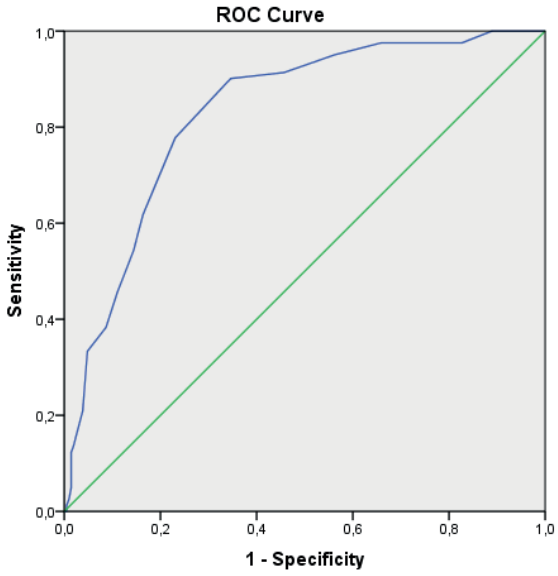
The cutoff scores with the highest Youden index were <20, <21 for MD, <24 for CI and <25 for MCI.

Only 50% of those with a positive MoCA (score <21) had MD (PPV), but 94% of those with negative tests were correctly identified as not having dementia (NPV) (table 3). Given the a priori likelihood of MD (28%) in this sample, a NPV of 94% represents a considerable improvement over chance. When using the MoCA for detecting CI (MD+MCI), 90% of the positive tests (<21) correctly identified CI. In clinical practice, a cutoff of <21 resulted in 90% of those with a positive MoCA having CI and 94% of those with a score of ≥21 not having Dementia.

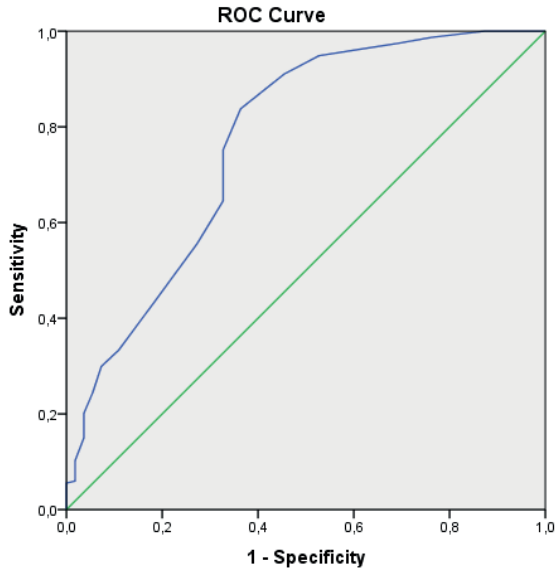
In example assessing 100 patients suspected of MD after initial assessment at a cutoff <21 would result in a 50% reduction of referrals compared to triaging only by initial assessment. The amount of FP would be 25 (of whom were 20 MCI), and 3 FN.

We further explored the distribution of the MoCA scores with a boxplot of the main groups and the MoCA scores by DSM IV diagnosis (figure 2). Of the demented patients, all of the DLB and mixed causes, and 75% of the vascular and Alzheimer patients scored <21. Three out of five patients with Alzheimer's that scored ≥21 appeared to have very high education (PhD degree). Of the FTD patients (*n*=4) 75% scored 21. The median MCI MoCA score was 21. Looking at the etiology of the MCI group, the neurodegenerative patients were responsible for most of the false positives (FP). More or less 50% of the depressed, bipolar and the schizophrenic patients diagnosed with MCI scored <21.

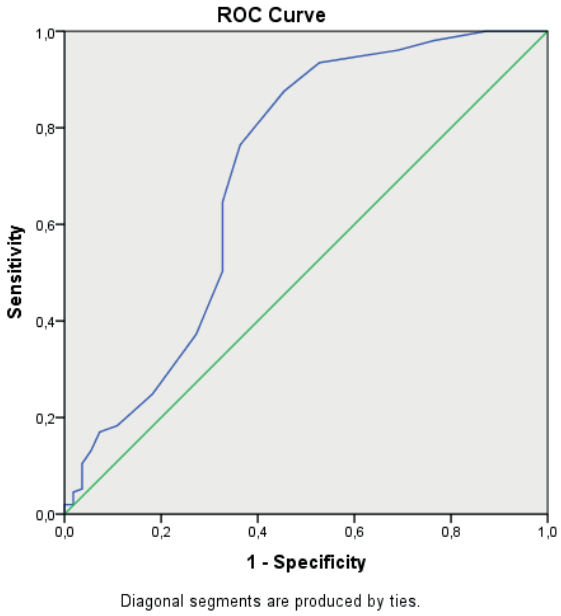
Figure 3 a, b, c. Results of ROC Analysis (*n*=292)



a. **Dementia (*n*=83) versus No-Dementia (MCI + SNoCI *n*=209)**



b. **Cognitive Impairment (Dem + MCI *n*=236) versus SNoCI (*n*=56)**



c. **MCI (*n*=153) versus SNoCI (*n*=56)**

Table 3. Area Under the Curve between variations of groups and their sensitivity, specificity, PPV and NPV at cutoff scores 26 and 21 with the best Youden index (*n*=292).

groups						CutOff <26				CutOff <21		
			AUC	SE	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Dem	vs	NoDem	.830	.026	98	17	31	95	90	65	50	94
Dem	vs	MCI	.810	.029	98	6	36	83	90	63	56	92
CI	vs	SNoCI	.770	.040	95	47	88	68	56	73	90	28
MCI	vs	SNoCI	.707	.048	94	47	83	72	37	73	79	30

Dem: Dementia; NoDem: No Dementia (MCI+SNoCI); MCI: Mild Cognitive impairment;

SNoCI: Suspected patients no Cognitive Impairment; CI; Cognitive Impairment (Dem+MCI).

AUC: area under the Curve; SE: Standard Error; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value.

Table 4. Sensitivity and Specificity at MoCA scores from 18 through 26

Cut-off value†	Sensitivity	Specificity MCI+SNoCI No Dementia	MCI	SNoCI
Dementia				
18	54%	86%	83%	93%
19	62%	84%	82%	89%
20	78%	77%	75%	82%
21	90%	65%	63%	73%
22	91%	55%	50%	67%
23	95%	43%	35%	67%
24	98%	34%	24%	64%
25	98%	24%	12%	55%
26	98%	17%	6%	47%
CI (Dem+MCI)				
18	30%			93%
19	33%			89%
20	43%			82%
21	56%			73%
22	65%			67%
23	75%			67%
24	84%			64%
25	91%			55%
26	95%			47%
MCI				
18	17%			93%
19	18%			89%
20	25%			82%
21	37%			73%
22	50%			67%
23	65%			67%
24	77%			64%
25	88%			55%
26	94%			47%

†(MoCA-D below score)

Dem: Dementia; MCI: Mild Cognitive impairment; SNoCI: Suspected patients no Cognitive Impairment; HC: Healthy Controls; CI; Cognitive Impairment (Dem + MCI).

4.4 Discussion

Our aim was to test the criterion validity of the MoCA for MCI and MD in patients suspected of CI and intended to be referred for a comprehensive diagnostic route in an old age psychiatry memory clinic.

We did this because, to our knowledge, no previous study has looked at the criterion validity of the MoCA being used as an add-on i.e. as a (secondary) objective test, after initial assessment in this setting. This is important as it involves a considerable and

growing number of patients seen each year and because it is likely that the performance of the MoCA is different across settings. Besides, a lot of the former studies were carried out with healthy controls as comparisons causing spectrum-bias.

As would be expected, the mean MoCA scores differed significantly between patients with MD, MCI and SNoCI. However within all three groups, the range was substantial – particularly within the MCI group –, making it difficult to differentiate between the three groups using an individual MoCA score as some scores overlap into the other groups. As can be seen in the boxplot (figure 2b), the range has not merely a psychiatric cause as the MCI neurodegenerative group (MCI-ND) have an even wider range.

The mean scores of the MD and MCI groups were comparable to those reported in the literature and demonstrate that our results have external validity (*Mocatest.Org*). Our control group scores were lower than those in the original and most other validation studies that used healthy controls, but we showed in an earlier study that the use of healthy individuals as controls resulted in a high mean MoCA score, leading to an unrealistically good specificity and PPV (Dautzenberg et al., 2020; Noel-Storr et al., 2014). Our mean MoCA scores were very similar to all patient groups referred to a memory clinic, this included the comparison group (Larner, 2012). Another explanation for the lower scores of our comparison group, and hence a lower specificity, is the psychiatric "comorbidity" which is known to decrease the MoCA score on its own (Blair et al., 2016; Ramírez et al., 2014; Wu et al., 2017).

Our "low" SNoCI specificity of 47% concurred with another memory clinic study, where the comparison group consisted of referred subjects with memory loss complaints including psychiatric illnesses (Smith et al., 2007).

Testing the MoCA in our memory clinic setting revealed a good (Fischer et al., 2003) AUC (0.83) when differentiating between demented and non-demented, but with mediocre specificity (65%). This implies that the MoCA could accurately find most demented patients in a group suspected of CI (sensitivity 90%, <21), but a substantial amount of non-demented patients also scored below this cutoff (of whom 79% are MCI), making it unsuitable for diagnostic purposes but good as a screening tool for MD. This is also demonstrated in the poor PPV of 50 at a cutoff <21.

When wishing to use the MoCA to identify those in need of further cognitive work-up (triage), a high NPV is needed to safely exclude patients who do not need further diagnostic work-up.

Given the results of our study, we recommend using the MoCA to exclude MD if someone scores 21 or above. Taking clinical and demographic factors such as FTD or very high levels of education into account (respectively 4.9% and 3.7% of our MD patients), the chance of this patient having MD is very low (NPV>94%). Although the absolute numbers of these outliers in our study were low, it confirms that MoCA tests results of patients with FTD or high education are prone to be false negative.

The overlapping range of MoCA scores between groups in this study could be explained by individual differences such as FTD or PhD degrees (resulting in higher scores in the MD group), and poor motivation/concentration/attention due to mania or severe depression and schizophrenia (resulting in some lower scores in those with psychiatric illnesses) (Blair et al., 2016; Ramírez et al., 2014; Wu et al., 2017; Yoon et al., 2017). This underscores the importance of taking demographic and clinical factors into account when interpreting the MoCA results and not simply relying on the score, which is further emphasized by the finding that the MoCA score range of the SNoCI in this study (12-30) is smaller compared to our previous study (5-30) where the results of the initial assessment were not taken into account (Dautzenberg et al., 2020).

It is reported that half of the patients with mild depression referred with cognitive complaints scored below 26 on the MoCA in a memory clinic (Blair et al., 2016). Another study reported that admitted schizophrenic patients had a mean MoCA score of 22 and 70% scored <26 (Wu et al., 2017). Their MoCA score was independent of their clinical state. A negative correlation between the cognitive part of the PANSS (assessing symptoms of schizophrenia) and the MoCA was found in another study with a mean MoCA of 23 (Ramírez et al., 2014). Our results, as underscored in the boxplot, are in line with these studies and showed the individual effect of psychiatric comorbidity.

If one excludes all psychiatry, as often happens in studies, the higher scores of the comparisons will result in a better specificity, but would no longer represent the clinical reality. Referrals with cognitive complaints during, or possibly due to, psychiatric illnesses is the clinical reality and need to be differentiated. As neurodegenerative causes could still be a comorbidity or even the cause of this psychiatric illness considering their age. Excluding these patients could lead to a delayed diagnosis as (especially) depression or psychosis can be seen during early stage dementia. To find the optimal cutoff value we used the objective Youden J index, although the object and the setting can result in a different 'best' cutoff score. For differentiating between MD and no-dementia, cutoffs of <21 and <20 result in the same Youden score – however, the <21 cutoff has a sensitivity of 90% compared to 78% at <20, favoring the former when used as a screener. When

identifying MCI, we favor a cutoff of <26, with a sensitivity of 94%, compared to a cutoff of <25 with a sensitivity of 88% despite the latter having a better Youden index by 2%.

Our study showed that the MoCA was excellent at confirming normal cognition amongst patients suspected of CI and thereby very helpful in triaging, i.e. the decision if they indeed need to be referred to a memory clinic. Depending on the accessibility of further diagnostic workup, one can vary the cutoff score and thereby change the amount of FP and FN. Being aware of the patient's high education level or FTD-symptoms would even lower the FN as shown in this study.

A strength of our study was that the cohort consisted of patients where the clinician wanted further diagnostics. Not merely the patient's (lack of) subjective complaints was decisive, nor psychiatric comorbidity for in- or exclusion. This cohort design comes with a limitation: all MoCA scores were included independent of the compliance during the MoCA assessment. Clinical judgment could also be used to lower the FP, especially those lacking motivation during the assessment. Again, one should be cautious of not missing MD with depressed or psychotic symptoms. Even if one could rule out all psychiatric causes of MCI before referral, our findings showed that 50% of the MCI-due to a neurodegenerative process (MCI-ND) scored below 21. Despite their low MoCA scores, these patients still clinically didn't have dementia, as they were mostly IADL independent (GDS score of 3). Because by Dutch law only a psychiatrist can initiate compulsory referrals and our old age psychiatry led memory clinic offers also non-pharmacological home therapies this results in more advanced dementia referrals (severe dementia, BPSD and compulsory referrals), including from other memory clinics, to our clinic. Hence the fast numbers of excluded patients with a clear diagnosis of severe dementia. This could be an explanation why, after applying the exclusion criteria of this study, the prevalence of Alzheimer's dropped from 61% at referral to old age psychiatry to 33% (23/83) in the study population. This could be a possible limitation of our study as we did not include all patients and that this (may have) influenced our findings, as we deliberately excluded all obvious and known causes and severe CI, e.g. BPSD and severe dementia (GDS ≥5). However, this may also be considered a strength of this validation of the MoCA where only patients suspected of CI – excluding the extremes of the spectrum as STARDdem dictates – were included. We believe that this is closer to the clinical reality as a triage tool has no added value for patients with obvious clinical symptoms of severe dementia. They don't need triaging but need further work-up in case etiology has still to be identified. This also counts for the excluded patients with delirium, substance abuse or brain injury. Even though this comes with a risk of having omitted cases of vascular and/or mixed dementia.

If one considers only the SNoCI as the absolutely unwanted referrals to a memory clinic and the MCI not, as they have a higher risk of developing dementia, the specificity raises to 73% and the PPV to 90% (<21). However, the degree of being unwanted depends on the availability of resources, especially in mid and low income countries where most demented live and up to 90% are not diagnosed (Alzheimer's Disease International, 2018).

It is still being debated whether the benefits of screening (e.g. early detection allows the improvement of clinical care and management of dementia) (Baune & Renger, 2014; Pendlebury et al., 2015) outweigh potential harms (e.g. false positive referrals with emotional and financial burden) (Borson et al., 2013; Brunet et al., 2013; Burn et al., 2018; Le Couteur et al., 2013; Lin et al., 2013). The MoCA also comes with its cost: training and assessing-time. Still there are more and more advocacy groups or policy makers that recommend screening, especially for higher risk populations (Alzheimer's Disease International, 2018; Borson et al., 2013; Cordell et al., 2013; Janssen et al., 2017; Pendlebury et al., 2015). As our patients were believed to be at high risk, and their quality of life seems not to be altered by the assessment(Janssen et al., 2019; McCarten et al., 2011), the use of a short triaging test prior to referral to our memory clinic seems beneficial and may add to a better use of limited resources (Janssen et al., 2019; McCarten et al., 2011). One might question if our setting is comparable to other (non-old age psychiatry) memory clinic settings, as our prevalence of MCI was high due to psychiatric diseases causing cognitive complaints. But we showed that by leaving out all psychiatric causes of MCI, the median stayed 21. A lower prevalence of MCI would result in better PPV, without changing the sensitivity.

4.5 Conclusions

Given the above limitations, our overall conclusion is that the MoCA is not suitable for differentiating dementia, but that it is a good tool for screening for MD and MCI even in the old age psychiatry setting and has added value for triaging who is not in need of a specialized diagnostic route. This applies especially in settings where memory clinics are scarce and efforts have to be made to reduce the absolute number of referrals for full diagnostic work-up, without missing those patients in need of further assessment. 90% of those with a MoCA score of <21 will have *CI* (MD *and* MCI), while 94% of those with a MoCA of ≥21 will not have *dementia*.

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SECTION

The MoCA in clinical practice

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CHAPTER

The Montreal Cognitive Assessment (MoCA) with a double threshold: improving the MoCA for triaging patients in need of a neuropsychological assessment

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International Psychogeriatrics 2022 Jun;34(6):571-583 34:6, 571–583

doi:10.1017/S1041610221000612

ABSTRACT

Objectives:

Diagnosis of patients suspected of mild dementia (MD) is a challenge and patient numbers continue to rise. A short test triaging patients in need of a neuropsychological assessment (NPA) is welcome. The Montreal cognitive assessment (MoCA) has high sensitivity at the original cut-off <26 for MD, but results in too many false positive referrals in clinical practice (low specificity). A cut-off that finds all patients at high risk of MD without referring too many patients not (yet) in need of an NPA is needed. A difficulty is who is to be considered at risk, as definitions for disease (e.g. MD) do not always define health at the same time and thereby create subthreshold disorders.

Methods:

In this study we compared different selection strategies to efficiently identify patients in need of an NPA. Using the MoCA with a double threshold tackles the dilemma of increasing the specificity without decreasing the sensitivity, and creates the opportunity to distinguish the clinical (MD) and subclinical (MCI) state and hence to get their appropriate policy.

Setting/participants: patients referred to old age psychiatry suspected of cognitive impairment that could benefit from an NPA (n=693).

Results:

The optimal strategy was a two-stage selection process using the MoCA with a double threshold as an add-on after initial assessment. By selecting who is likely to have dementia and should be assessed further (MoCA<21), who should be discharged (≥26) and who's course should be monitored actively as they are at increased risk (21<26).

Conclusion:

By using two cut-offs the clinical value of the MoCA improved for triaging. A double-threshold MoCA not only gave the best results; accuracy, PPV, NPV and reducing false positives referrals by 65%, still correctly triaging most MD-patients. It also identified most MCIs whose intermediate state justifies active monitoring.

5.1 Introduction

More diagnostic effort is recommended by the Alzheimer's society because early recognition of dementia allows for timely interventions and better quality of life for the patients (Borson *et al.*, 2013;). However, the (clinical) reality has its limitations.

The diagnosis of patients with suspected mild dementia (MD) is challenging, and the number of patients continues to rise.

It is difficult to differentiate who has MD based on anamnesis alone. Subjective complaints and reports from informants often do not correspond to objective impairments (Schouws *et al.*, 2012; Pendlebury *et al.*, 2015; Ryu *et al.*, 2020).

Specialised diagnostic facilities are needed but will become overloaded by the number of referred patients in the near future. Most countries already have diagnostic challenges (Alzheimer's Disease International, 2018), including a lack of financial or staff resources for a time-consuming comprehensive neuropsychological assessment (NPA). An accurate short screening test to identify patients with a (high) risk of MD, i.e., those in need of an NPA, is therefore necessary. A difficulty is who is to be considered at risk as definitions for disease (e.g., MD) do not always define health at the same time and thereby create subthreshold disorders (Helmchen and Linden, 2000). Cognitive functioning is a state on a continuum with dementia on one end and no cognitive impairment (NoCI) on the other end of the extremes. Classifications define these states, therefore creating double thresholds. In-between, there is an area in which the patient is in an intermediate state and at risk, e.g., mild cognitive impairment (MCI), of which approximately 40% worsens 40% stabilises and 20% recovers (Gauthier *et al.*, 2006; Julayanont *et al.*, 2014; Canevelli *et al.*, 2016).

Given the wide range of outcomes of MCI and the large numbers involved, it is essential to be able to differentiate patients with MCI from those with MD and NoCI (Gauthier *et al.*, 2006). In particular, in an old age psychiatry setting, there is a high correlation between psychiatric conditions (American Psychiatric Association, 2013) (including psychotropic medication and substance abuse) and MCI that does not necessarily worsen over time (Julayanont *et al.*, 2014). These MCI cases deserve their own policy. An elaborate diagnostic route (including biomarkers/MRI) is often not yet necessary, but they should not be discharged either. A NPA comes to mind as a compromise. However, limited resources warrant the restraint of false positive (FP) referrals for an NPA to avoid potential harm due to unnecessary emotional and financial burden (Borson *et al.*, 2013; Burn *et al.*, 2018; Davis *et al.*, 2015). Although early identification of neurocognitive disorders is advocated

spending resources wisely is as important, giving the ones the most in need priority (*Alzheimer's Disease International 2018*; Borson *et al.*, 2013). This implies that patients at highest risk (taking into account the age or speed of onset in combination with the degree of impairment) should be referred for an elaborate specialised diagnostic route. The cognitive functioning of patients considered to be at lower risk (e.g., with psychiatric disorders) should be assessed in the best available way, depending on the resources. When the scarce and time-consuming gold standard i.e. an NPA, is less available the assessment of the cognitive functions could be done with a short, validated test. In our opinion, this should include reassessment with this test, as it is easy to perform and takes limited time to administer, i.e., active monitoring. Therefore, it is important to use screening instruments that can detect both MD and MCI.

The Montreal Cognitive Assessment (MoCA) was developed as a short screening tool for MCI and MD (Nasreddine *et al.*, 2005) and validated in at least 35 different languages and even more settings. Most of these studies can be found on the MoCA-test website (*mocatest.org*). At the original proposed cut-off of <26, the sensitivity for correctly screening patients with MCI (90%) and MD (100%) is very good (Nasreddine *et al.*, 2005). Although it has been repeatedly shown to be superior to the MMSE in identifying MCI (Folstein, *et al*., 1975; Pinto *et al.*, 2019), the MoCA still has its limitations as a triaging tool. Its ability to identify people with NoCI (specificity) is criticised in clinical practice because specificity varies due to clinical and demographic reasons (Davis *et al.*, 2015). Frequently reported examples are age, education, rural environment, ethnic or cultural background (including race in some countries), substance abuse and psychiatric diseases (*mocatest.org*). It is repeatedly suggested to lower the cut-off with higher specificity as a result (O'Driscoll and Shaikh, 2017; Carson *et al*. 2018;Dautzenberg *et al*., 2020). Nevertheless, the MoCA with a lower cut-off is still not suitable for identifying MD as a stand-alone assessment of referred patients to an old age psychiatric clinic (Dautzenberg *et al*. 2020; Korsnes, 2020), or as an assessment of referred patients to its memory clinic (Smith *et al*. 2007; Dautzenberg *et al.,* 2021) because the positive predictive value (PPV) is never sufficient (Carson, *et al*., 2018). Its high sensitivity makes it a good screener, finding most MD patients. The high negative predictive value (NPV) for appropriately discharging NoCI patients, is promising, although for triaging those who need a scarce NPA, moderate specificity gives too many false positives (FPs).

Double cut-offs are reported in the literature as a solution by using one threshold for health and one for disease (Batelaan *et al.*, 2007; Swartz *et al.*, 2016; Landsheer, 2020; Thomann *et al.*, 2020). Especially where classifications create subthreshold disorders,

regardless of whether these are disorders in their own right or are merely (minor) forms of major disorders (Batelaan *et al.*, 2007). Either way MCI is not (yet) dementia.

A double-threshold MoCA offers the possibility to distinguish clinical and subclinical states according to their appropriate domain and thus to implement different policies. Previous studies have shown that almost no patients with MD or even MCI will score ≥ 26, the originally proposed cut-off of the MoCA, therefore indicating health (i.e., NoCI) (Nasreddine *et al.*, 2005; Davis *et al.*, 2015; Carson *et al*., 2018; Dautzenberg *et al*., 2020, 2021; Korsnes, 2020). The number of FPs below this cut-off is too large to have a full work-up. 'Reducing the risk of FP is important (Davis *et al.*, 2015). In a memory clinic setting, half of the depressed patients scored below 26 (Blair *et al.*, 2016; Dautzenberg *et al*., 2021). Other studies showed that the majority of patients with affective- psychotic- or neurotic disorders scored between 20-26 on the MoCA, while the majority of the organic disorders scored <19 (Gierus and Mosiolek, 2015; Dautzenberg *et al*., 2021; Korsnes, 2020). By using a lower (second) cut-off for referral (using the highest Youden index for MD in this cohort; <21) (Dautzenberg *et al*., 2020), FPs will decrease, but this will also increase the false negatives (FNs). This could be compensated for by actively monitoring all these patients with a score from 21 to 26, reducing unnecessary referrals (FP), but still allowing those patients at high risk of MD to be monitored (FN).

A recent study by Landsheer demonstrated that using a double threshold for the MoCA improves clinical classification and that using an uncertainty interval (21 to 26) reduces the effect of prevalence on MoCA performance (Landsheer, 2020).

Other studies on double thresholds aimed to improve classification accuracy by stratifying the population based on normative data (Oren *et al.*, 2014; Tan *et al.*, 2014; Borland *et al.*, 2017) or stratifying the outcome, of certain or uncertain test results (Swartz *et al.*, 2016; Landsheer, 2020; Thomann *et al.*, 2020). They do not separate the three distinct cognitive states, i.e., MD versus MCI versus NoCI.

In our study, however, we wanted to introduce *three* policies, matching the *three* diagnostic entities of cognitive functioning, to improve the MoCA's potential as a triaging tool.

Although the use of the MoCA in this way feels intuitive, to our knowledge, no results have been presented before on the MoCA with a double threshold separating all three distinct stages and analysing the consequences of subsequent policies.

Especially in old-age psychiatry there are many inconclusive MoCA scores due to age (60+) and psychiatric comorbidities (including psychotropic medication), i.e., from 21

to 26. Therefore, we studied the policy of 'active monitoring' in this population as an intermediate option.

We used data from our cohort of an old age psychiatric setting (Dautzenberg *et al*., 2020, 2021), where referrals, at least in the Netherlands, include patients with cognitive, behavioural and psychiatric symptoms that may result from neurodegenerative diseases, but also from other psychiatric disorders. The standard is that after an initial assessment, it is decided who could benefit from an extensive cognitive diagnostic route at our memory clinic.

We aim to demonstrate the advantages of using a double-threshold MoCA to triage patients in need of an NPA. Therefore, we compare different selection strategies, including the double threshold, to efficiently select patients in need of an NPA (i.e., MD), those who are not (NoCI) and patients who should be actively monitored (MCI). We rate the strategies according to their accuracy and the number of referrals for an NPA that result in as few false negatives (FNs) as possible.

The compared selection strategies for referral to an NPA are as follows:; an initial assessment only (without the use of an objective test, i.e., the MoCA), the MoCA as a stand-alone (i.e., without clinical judgement), or the MoCA as an add-on after the initial assessment (i.e., as a two-stage screener). The MoCA strategies are compared when using single and double thresholds.

5.2 Methods

5.2.1 Study sample

The cohort (*n*=693) was taken from a previously reported validation study of the MoCA for patients referred to an old age psychiatric service in Utrecht, the Netherlands, as described in detail elsewhere (Dautzenberg et al., 2020). In short, all newly referred patients to our clinic were eligible for the study if they were capable of giving written informed consent. Therefore, patients with severe dementia (Global Deterioration Scale (GDS) ≥6) (Reisberg *et al.*, 1982), and Behavioral and Psychological Symptoms of Dementia (BPSD) as a reason for referral and compulsory referrals were not eligible (*n*=1337). To resemble a clinical screening population, Standards for Reporting Diagnostic Accuracy (STARD/STARDdem) (Noel-Storr *et al.*, 2014; Bossuyt *et al.*, 2015) require we excluded patients with an obvious diagnosis of dementia (GDS ≥5), a recent history of substance abuse (<1 year), delirium (<6 months), or acquired brain injury including CVA

or TIA (*n*=174). The patients suspected of having cognitive impairment after the initial assessment were referred to our memory clinic (*n*=290) (figure 1). All of these patients underwent a comprehensive cognitive diagnostic route for cognitive impairment using a consensus-based diagnosis, following international criteria as a reference standard with an NPA and when applicable, CT/MRI- imaging and cerebrospinal fluid (CSF) analysis (CBO Geriatrie, 2014). They were classified as MD, MCI (including psychiatric aetiologies) or NoCI (including subjective complaints, mostly psychiatric patients without objective cognitive impairment).

For the strategic selection route comparison, we included all eligible referred patients (*n*=693), including those not suspected of cognitive impairment (*n*=403). The latter were followed for at least 2 years to compensate for not having an NPA to exclude conversion to any DSM IV/5 (American Psychiatric Association, 2000, 2013) cognitive diagnoses after the initial assessment. Three of them were diagnosed with cognitive impairment during follow-up and were considered inconclusive as it is not certain if these impairments manifested before or after initial assessment. To be conservative, we classified these three as FN MD.

All participants gave their informed consent. Data are available upon request.

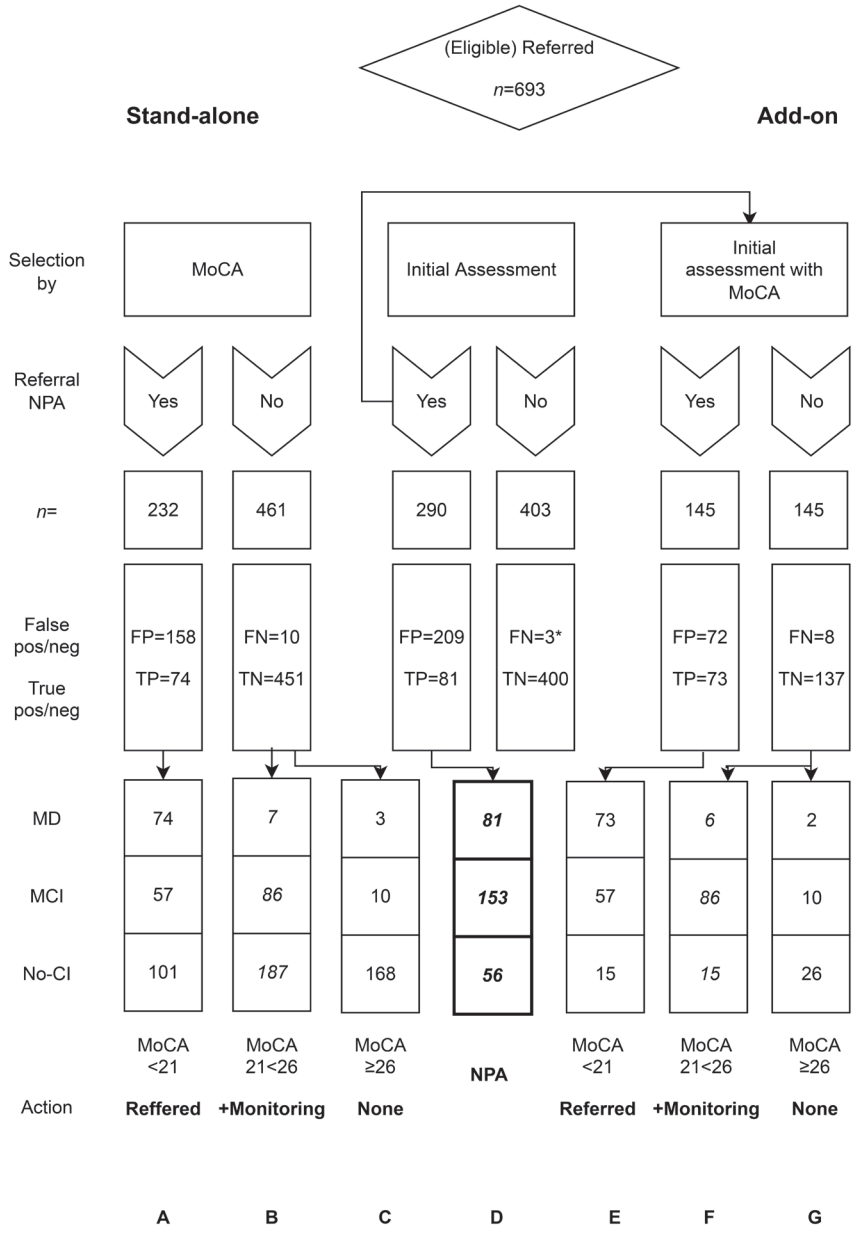

Figure 1. Flowchart and results of the different selection strategies.

MoCA: Montreal Cognitive assessment.

NPA: comprehensive NeuroPsychological Assessment.

FP: False Positive; FN: False Negative; TP: True Positive; TN: True Negative.

*: FN during follow up.

5.2.2 Measurements

Initial assessment

The initial assessment was completed by old age psychiatrists (*n*=4, having at least 8 years of practical experience in 2008) and included a laboratory test, medical and functional history from a next of kin and an investigation of Instrumental Activities of Daily Living (IADL) performed by a psychiatric nurse practitioner with a home visit. The 15-item Geriatric Depression Scale (GDS15) (Yesavage and Sheikh, 1986) and the Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) were also administered during this time.

Diagnostic test

All of the referred participants were assessed with a MoCA as soon as possible but within 3 months of referral by a trained psychiatric nurse practitioner. This was independent of the diagnostic procedure.

The MoCA consists of one page that covers the cognitive domains of executive function and visuospatial abilities, naming, short term memory, attention and working memory, language, concentration, verbal abstraction and orientation. It can be administered within 10 minutes and the maximum score is 30, which indicates that no errors were made. Correction for low education effects was done, according to the instructions, by adding one point to the total of patients with 12 years of education or less. The suggested best cut-off for the diagnosis of dementia was a score of 21 (<21) and <26 for MCI, in both old age psychiatry and memory clinic settings (Dautzenberg *et al*., 2020, 2021).

Reference test

The reference test was the diagnosis determined at multidisciplinary meetings, including an old age psychiatrist, neuropsychologist and geriatrician. The diagnosis of MD, MCI or NoCI was supported with at least a 4-hour NPA. The NPA included multiple tests in the domains of memory, attention, executive function, fluid intelligence and language capacities (for details please see Dautzenberg *et al*., 2020). The diagnoses were made in consensus and in accordance with the MCI criteria as proposed by an international consortium (Winblad *et al.*, 2004; Gauthier *et al.* 2006), or the Dutch guideline on dementia (CBO Geriatrie, 2014). This guideline covers the criteria of -DSM IV/5 and the international criteria for dementia. The results of the MoCA were not used to diagnose MCI or dementia. The Dutch translation of the DSM 5 was introduced in the Netherlands at the end of the study of the cohort (2017). All patients were classified according to DSM IV for the purpose of this study.

Table 1. Key demographic and clinical characteristics

	Dementia (a)	MCI (b)	NoCI (c)	Total Referred	Statistic difference p<0.001
Variable / *n*	**84**	**153**	**456**	**693**	
Age	77.3	73.9	71.3	72.5	
(SD)	(7,5)	(8.0)	(7.3)	(7.8)	a>b>c
range	59-94	53-93	58-92	53-94	
Education <12 (%)	52	53	43	47	No sig.
Sex F (%)	63	57	63	62	No sig.
GAF	52	57	52	53.3	a,c<b
(SD)	(10.2)	(12.8)	(12.4)	(12.3)	
range	30-80	20-90	20-95	20-95	
GDS15	6.6	7.7	8.6	8.4	No sig.
(SD)	(4.9)	(4.7)	(4,3)	(4.3)	
range	0-15	0-14	0-15	0-15F	
MoCA	16.5	20.9	23.5	22.1	
(SD)	(4.0)	(3.8)	(4.2)	(4.7)	a<b<c
range	5-26	3-28	3-30	3-30	

Groups a,b and c were compared with ANOVA, education and sex were compared with a Chi2 test.

MCI: Mild Cognitive Impairment; NoCI: No Cognitive Impairment; GAF: Global Assessment of Functioning; GDS15: Geriatric Depression Scale 15 question version; MoCA: Montreal Cognitive Assessment.

5.2.3 Statistical Analyses

The demographic results (table 1) were compared within the patients with MD, MCI or NoCI using Statistical Package for the Social Sciences (SPSS, version 22; SPSS Inc., Chicago, IL); Chi2 test to compare sex and education. ANOVA was used to compare age, GAF, GDS15, and MoCA scores followed by a least significant difference (LSD) post hoc test.

The previously reported area under the curve (AUC) calculations using receiver operating characteristic (ROC) analysis were used to find the best cut-off scores (Dautzenberg et al., 2020, 2021) for both settings (table 2).

We reported the false positives (FPs), false negatives (FNs), true positives (TPs) and true negatives (TNs) of the different selection strategies to judge the clinical effects (figure 1). The positive predictive value (PPV =TP/(TP+FP)), negative predictive value (NPV =TN/(TN+FN)) and accuracy (ACC=(TP+TN)/(TP+TN+FP+FN)) were calculated (table 3). However, with these indicators, it is impossible to weigh the FN and FP rates separately, which is a disadvantage, and absolute quantities can provide more insight when diagnostic routes are compared (Glas *et al.*, 2003). Therefore, we also expressed the results of the selection strategies in absolute numbers (figure 1, table 3 and 4) of patients who were to

be referred (figure 1; column A, E), those who were to be observed (B, F), who were not (C, G) and the reference diagnoses (D). As the purpose of the study is to reduce the number of FP referrals without discharge a MD patient, we considered the observed MD, MCI and NoCI as TP, TN and TN, respectively. The calculation of the indicators for the two-stage strategy included the effects of the initial assessment (e.g. adding the 400TN and 3*FN to columns E, F, G).

Table 2. Area Under the Curve between variations of groups and their sensitivity and specificity at cut-off scores 26 and 21, often used in literature. Stand-alone (*n*=693) or add-on (*n*=290).

groups				AUC	SD	Cutoff <26		Cutoff <21	
						Sens	Spec	Sens	Spec
MD	vs	NoDem	(*n*=693)	.865	.018	.975	.292	.901	.740
MD	vs	NoDem	(*n*=290)	.830	.026	.975	.173	.901	.654
MD	vs	MCI	(*n*=693)	.810	.029	.975	.065	.901	.627
MD	vs	MCI	(*n*=290)	.810	.029	.975	.065	.901	.627
CI	vs	NoCI	(*n*=693)	.765	.018	.949	.368	.556	.778
CI	vs	NoCI	(*n*=290)	.770	.040	.949	.473	.556	.727
MCI	vs	NoCI	(*n*=693)	.702	.022	.935	.368	.373	.778
MCI	vs	NoCI	(*n*=290)	.707	.048	.935	.473	.373	.727

MD: Mild Dementia; NoDem: No Dementia (MCI+NoCI); MCI: Mild Cognitive impairment; NoCI: Referred patients no Cognitive Impairment; CI; Cognitive Impairment (Dem + MCI).

Stand-alone (n=693): all referred patients without judgement of initial assessment.

Add-on (n=290): only those patients suspected of CI after initial assessment. All referred to memory clinic.

5.3 Results

5.3.1 Demographic findings

The main demographic and clinical characteristics of the study group are listed in table 1.

The significant differences in age and sex are representative of the demographics of an old age psychiatry setting and are substantiated elsewhere (Dautzenberg et al., 2020).

The GAF score was the highest in the MCI group, as expected because these patients have the least severe symptoms, given the high number of MCI patients without any other psychiatric conditions (50%), whereas almost all patients in the NoCI had one or more psychiatric diagnoses (Dautzenberg *et al*., 2020).

Table 3. Results of the selection strategies.

		NPA	FN	FP	TP	TN	PPV	NPV	ACC	DIF	Column Fig 1.
		n	*n*	*n*	*n*	*n*	%	%	%	%	
	Cut-off's										
I.A.	n/a	290	3	209	81	400	27.9	99.3	69.4	n/a	D
MoCA	<26	512	3	431	81	178	15.8	98.3	37.3	+77	C
S.A.	<21	232	3+7	158	74	451	31.9	97.8	75.8	-20	A
	21<26	232	3	158	74+7^	451	33.9	99.3	76.8	-20	B
MoCA	<26	252	2+3*	173	79	36+400*	31.3	98.9	74.3	-13	G
A.O.	<21	145	8+3*	72	73	137+400*	50.3	97.9	88.0	-50	E
	21<26	145	2+3*	72	73+6^	137+400*	52.3	99.1	88.9	-50	F

*****including FN/TN of Initial Assessment.

^including the observation group

I.A.: Initial Assessment. MoCA: Montreal Cognitive Assessment. S.A.: stand-alone. A.O.: add-on.

NPA: referred for a Neuropsychological assessment. FN: False negative. FP: False Positive. TP; True Positive.TN: True Negative. PPV: Positive Predictive Value. NPV: Negative Predictive Value. ACC: Accuracy. DIF: difference in referrals compared to I.A.

5.3.2 Single threshold

The initial assessment resulted in 290 referrals for NPA (figure 1, column D). An accuracy of 69% was achieved for detecting MD (table 3), with 3 FNs. Using a single MoCA threshold of <21 to select those requiring an NPA resulted in a decrease in referrals but an increase in FNs compared to the initial assessment (Columns A and E). However, this resulted in an improvement in their accuracy (table 3). When the MoCA was used as an add-on to screen the 'patients not suspected after initial assessment' (*n*=403: table 4 d, calculations not shown), the accuracy deteriorated to 57% by adding 87 referrals to the initial set of 290 referrals, resulting in a total of 377 referrals (including 297 FPs).

Comparing the PPVs and NPVs of the different selection strategies at a cut-off <21 for MD, we found a substantial increase in PPV and only a slight decrease in NPV when the MoCA was used as an add-on.

When the cut-off was raised to <26 for detecting MD per strategy (columns C, G), the FNs decreased but with a substantial increase in referrals, which decreased the PPV and ACC.

Table 4 (**a**, **b**, **c** and **d)**. Cross tables of the different strategies.

a

	Initial assessment stand-alone		**(Fig 1:column D)**
	refer	**dismiss**	
MD	81	3	84
MCI	153	0	153
No-CI	56	400	456
	290	403	693

b

	MoCA stand-alone			**(Column A,B,C)**
	refer (<21)	**observe (21-26)**	**dismiss (≥26)**	
MD	74	7	3	84
MCI	57	86	10	153
No-CI	101	187	168	456
	232	280	181	693

c

	MoCA Add-on	**after**	**Positive initial assessment**	**(Column E,F,G,)**
	refer (<21)	**observe (21-26)**	**dismiss (≥26)**	
MD	73	6	2+3	84
MCI	57	86	10	153
No-CI	15	15	26+400	456
	145	107	441	693

d

	MoCA Add-on	**after**	**Negative initial assessment**	**(not shown in fig 1)**
	refer (<21)	**observe (21-26)**	**dismiss (≥26)**	
MD	1+81	1	1	84
MCI	0+153	0	0	153
No-CI	86+56	172	142	456
	377	173	143	693

5.3.3 Double threshold

The single threshold dichotomy reported above had a binary outcome: referral for NPA or no referral. This is not consistent with clinical practice, where an intermediate strategy of 'keeping the patient under observation' or 'active monitoring' is often used.

The use of two cut-off scores: <21 invitation for NPA, 21≤ active monitoring <26; no follow-up ≥26 gave a more differentiated result (columns B, F).

The double-threshold MoCA as an add-on for suspected patients after initial assessment (column F) resulted in 5(2+3*) instead of 11 MD (column E) patients with MD not undergoing a comprehensive diagnostic route, without the increase in FP referrals. This resulted in the highest accuracy (89%), PPV (52%) and NPV (99%). However it would mean that 107 patients need to be reassessed.

5.4 Discussion

Limited diagnostic resources and rising patient numbers present challenges in MD diagnostic procedures. It is necessary to differentiate patients to focus scarce diagnostic resources on those who need them most. Therefore, we compared different strategies, including a double-threshold MoCA. Our results confirm that an objective test can have added value. However, how and when the MoCA was used gave different results.

All the strategies we tested were able to find most of the patients with MD. Judgement by only the TP/FN is not sufficient, as the FPs differs substantially (figure 1/table 3). Using merely initial assessment (column D) gave the highest TP of the compared strategies, but the high amount of FPs complicates the diagnostic route: still 42% of all assessed patients were referred for a comprehensive diagnostic route. This is probably because clinicians try to avoid FNs. Especially without the assistance of an objective test, clinicians tend to refer subthreshold states earlier.

The single cut-off MoCA strategy did not solve the (sub)threshold dilemma. Although the low PPV and the very high NPV underscore that only a MoCA score above the cut-off (i.e., a negative MoCA) should be considered reliable and thus suitable to adjust clinical judgement, i.e., initial assessment (table 4d).

Using a MoCA as a second-stage screener with a score of 21 or higher (cut-off <21) to adjust initial assessment (column E) reduced the FP referrals for an NPA by 65% (to *n*=72 of 290) but increased the FN by 3.6 times to 13% of MD (*n*=11).

Using a double threshold with scores <21 identifying patients suitable for an NPA and ≥26 for discharging patients, i.e., indicating patients do not need an NPA or reassessment, not only gave the best results but also achieved two goals simultaneously. Not only compensating for the increase in FNs by monitoring most of the missed MDs but also at-risk intermediate state patients (MCIs), without increasing the number of referrals.

How to classify the different strategic selection outcomes for the accuracy calculations can be debated and depends on the setting and its target disease. Introducing a double threshold together with an intermediate state raises the dilemma of what is to be considered TP/FP or TN/FN. As these cells only exist in a 2x2 classification table, in our study, we created a 3x3 table (table 4b,c,d).
In addition to this theoretical classification problem, there is a clinical classification dilemma. There are multiple reasons to advocate (TP) or to be cautious (FP) with early MCI referrals and the debate is ongoing. Because of limited access to NPAs in most countries or rural areas and because MCI can also consist of aetiologies from which a patient can recover, we considered MCI an FP when a patient was referred for a comprehensive diagnostic route (therefore, MCI automatically became a TN for observation and discharging). Even though we understand that, with unlimited resources, one could consider (some of) the MCI-patients as TP when referred, as quality of life can improve by cognitive testing (Janssen *et al.*, 2019). Identifying this intermediate state to actively monitor MCI without giving them this demanding diagnostic route is another justification for using a double threshold. Intuitively, we would consider 21≤MCI<26 as TP (for monitoring); however, technically this is not possible, as MCI is already labelled as an FP when a patient has a score <21.

For dementia, a short assessment that differentiates MD from MCI with certainty would be preferred, but such a test is still not available. This is also true for the MoCA, as our results showed that our best PPV is still too low (52%) for a conclusive classification. Selecting those patients in need without missing one MD in the best way possible, without referring too many who are not (yet) in need of a memory clinic, is essential, i.e., triaging. These requirements were translated into our evaluation criteria of low absolute referral rates while still maintaining the highest possible sensitivity, i.e., no FNs and low FPs. Therefore, we judged the strategies by these values.

Of the strategies selecting MD, the double threshold add-on not only gave the highest accuracy (89%), PPV (53%), NPV (99%) and the lowest FPs with still acceptable FNs, it also creates the opportunity to monitor MCI and seems the preferred selection route (table 3, column F).

In addition to the accuracy calculations of our clinical example addressing the three cognitive entities as well as possible to their appropriate policy, as debated above, there are more arguments to be found in literature to use a double threshold for the MoCA.

First, a substantial number of MCI patients scoring below <21 on the MoCA are at very high risk of converting to MD, while those above this cut-off are considerably less at risk (Smith *et al*., 2007; Julayanont *et al.*, 2014; Dautzenberg *et al*., 2021).

Second, a double threshold for the MoCA also reduces the 'uncertain test scores' due to 'random classification errors'. These outcomes result from the distribution of the different diagnostic groups in the middle range MoCA scores (Landsheer, 2020; Thomann *et al.*, 2020). By applying an uncertainty interval, as these MoCA-scores are the most error prone, the PPV and NPV improve in the studied prevalence and become less dependent on the setting. Even if their study objective was not to identify the subthreshold state, the implementation is similar; applying an (uncertainty) interval improves the accuracy of the MoCA.

Third, as mentioned in the introduction, several variables are found to be of importance in different clinical populations and these can lead to an inflated rate of FPs particularly older age and lower education (Carson *et al*., 2018; Thomann *et al.*, 2020). Lifestyle and physical activity are found to significantly influence MoCA scores even more than age and education (Ihara *et al.*, 2013; Innocenti *et al.*, 2017). Although education (Wong *et al.*, 2015; Borland *et al.*, 2017; Pinto *et al.*, 2018), ethnicity (Rossetti *et al.*, 2011; Tan *et al.*, 2014; Wong *et al.*, 2015), race (Goldstein *et al.*, 2014; Tan *et al.*, 2014; O'Driscoll and Shaikh, 2017) and (rural) habitat (Goldstein *et al.*, 2014; Hilgeman, Boozer and Davis, 2018) are known factors, others debate that these factors are better represented by 'literacy in late life' (Sisco *et al.*, 2015). More important for our setting are the negative influence of substance abuse (Rojo-Mota *et al.*, 2013; Pugh *et al.*, 2018) or psychiatric diseases (Musso *et al.*, 2014; Gierus and Mosiolek, 2015; Blair *et al.*, 2016; Srisurapanont *et al.*, 2016; Wu *et al*., 2017; Korsnes, 2020).

The above enumeration shows that there are many reasons for heterogeneity affecting the MoCA score. It shows that a single cut-off rarely fits a pluriform clinical practice where many covariates influence the individual MoCA-score. A single cut-off is associated with substantially high rates of misclassification. Stratification was suggested for age and education as a solution (Oren *et al.*, 2014; Wong *et al.*, 2015; Borland *et al.*, 2017). However, stratification of patients is impracticable if one needs to take all the possible confounders into account.

Psychiatric comorbidities, such as depression or mania, only substantially influence the MoCA score in some individuals (Gierus and Mosiolek, 2015; Blair *et al.*, 2016; Dautzenberg *et al*., 2021; Korsnes, 2020), making beforehand stratification of these patients infeasible. This underscores that the MoCA should not be used as a stand-alone or overrule but should help clinical judgement as an add-on by knowing its strength (NVP, sensitivity) and weakness (PPV, specificity).

A strength of our study is that possible psychiatric causes of CI were not excluded, as (cloaked) psychiatry is the clinical reality in most settings, especially in old-age psychiatry. Another strength is that we used a clinical cohort setup by avoiding the extremes of the spectrum, such as community-based healthy controls, and severely demented including those with BPSD, following the STARDdem recommendations. Therefore, the cohort consisted of patients a clinician would consider screening for CI. Including severe dementia would give better results due to a higher dementia prevalence and lower MoCA scores but this is not the clinical reality.

Our setting on the other hand, is also a limitation, as referrals with BPSD and MCI caused by psychiatric aetiology will be higher than those in nonpsychiatric settings and will influence the prevalence of MD. However, our previous study showed that the mean MoCA score did not differ between neurodegenerative and psychiatric aetiologies of MCI (Dautzenberg et al., 2021).

A limitation of our study is the uncertainty of the number of FNs after initial assessment. The consecutive cohort design resulted in 'unsuspected patients after initial assessment' (*n*= 403) not receiving an NPA due to practicality and resource constraints. We minimised this flaw by following these patients for at least 2 years. Three out of 403 unsuspected patients progressed to CI, most likely new cases. This corresponds with the incidence of 6.6 males or 7.4 females in the 74-79 age group (Volksgezondheidenzorg.info, 2019). Nonetheless we labelled them as if they were FN at the initial assessment. As stated before clinicians tend to refer when in doubt to minimise their FNs, which adds to their low FNs in this study. This favours the add-on strategy, but it also mimics the clinical reality.

The acceptance of the amount of FN next to the availability of an NPA will influence where one puts the cut-off for referring to an NPA. Simply changing a single cut-off will not improve the number of classification errors (Landsheer, 2020). With a second cut-off for monitoring, one can consider the pros and cons of lowering sensitivity against the gain of specificity but avoid absolute or binary decision errors. We also considered the use of a third cut-off, meaning below a certain score no referral is necessary as dementia is surely

identified i.e., diagnosed, but this is not feasible. Even with high dementia prevalence (e.g., including the severe or known demented, although not the clinical reality), the PPV of this extra cut-off would increase but never to the needed PPV of 100%.

For settings similar to ours, we recommend the use of the double threshold as described of <21 and ≥26, as these cut-offs give the best results, including the Youden index (Dautzenberg et al., 2020, 2021). This corresponds with the most error-prone scores of the MoCA (Landsheer, 2020) and is consistent with another study in old-age psychiatry, in which 87% of patients with dementia scored <20 and 100% scored <23 on the MoCA (Korsnes, 2020). In addition, almost all MCI patients with low MoCA scores (<20) will develop MD whereas only half of the MCI patient above this score will convert in the near future (Julayanont *et al.*, 2014). Another study showed that 65% of their MCI patients with a score <26 did not convert to MD (Smith *et al*., 2007). This suggests that a double-threshold MoCA can separate low-risk MCI patients from very high-risk patients along with almost all patients with MD and benefit from a specialised diagnostic route.

Although our findings are not compatible with other settings, different settings may also benefit from a double-threshold MoCA. Whether it is to improve accuracy or because these settings have a more diverse population (and less uniformly distributed cognitive functioning). Even if one does not agree with our proposed policy because of a low prevalence of psychiatric diseases or easy access to specialised diagnostic routes in their setting. The 3 policies can easily be altered to fit once own setting, e.g., full memory clinic work up <21; 21< active monitoring with an NPA <26; and ≥26 watchful waiting with a MoCA.

As the MoCA can detect changes over time in MCI patients (Krishnan *et al.*, 2017) and remains stable among cognitively normal patients (Malek-Ahmadi *et al.*, 2018), active monitoring (21<26) can be done by reassessment with a MoCA, which has three versions avoiding a learning curve (Costa *et al.*, 2012; Nasreddine and Patel, 2016) and has a high retest reliability (Bruijnen *et al.*, 2020). Together with an interview on IADL, giving an improved model fit (Durant *et al.*, 2016) combined with an IQcode (De Jonghe, 1997), it can be administered in less than 30 minutes and could increase the overall diagnostic accuracy (Roalf *et al.*, 2013). The average time of an NPA was 9 h, including processing and feedback, at a cost of (in the Netherlands) €110/h. Therefore, the MoCA can not only reduce the stressful NPA waiting list but also avoid €1000 per FP and actively monitor those at risk less expensively.

5.5 Conclusion

To conclude, the optimal strategy for NPA referral is a two-stage selection process using the MoCA with a double threshold as an add-on after initial assessment. By selecting who is likely to have dementia and should be assessed further (MoCA<21), who should be discharged (≥26) and whose course should be monitored actively as they are at risk (21<26). This strategy not only gives the best results (accuracy, PPV, NPV) by referring most MD patients and reduces unnecessary FP referrals by 65%. It also identifies most MCIs whose intermediate state justifies active monitoring. By introducing a second cut-off, the clinical value of the MoCA improved.

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CHAPTER

Severe cognitive impairment associated with a high free, but therapeutic total concentration of valproic acid due to hypoalbuminemia in an older patient with bipolar disorder

6

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Journal of Clinical Psychopharmacology 2018 Jun;38(3):265-268.

doi: 10.1097/JCP.0000000000000872.

ABSTRACT

Objectives:

We present an elderly, bipolar patient with a high free concentration of VPA but (sub) therapeutic total concentration VPA due to hypoalbuminemia (14-25g/l) leading to reversible severe cognitive impairment.

Methods:

Valproic acid (VPA) is largely bound to serum proteins (80-95%) particularly albumin, with a saturable binding capacity. In hypoalbuminemic patients, protein binding of VPA will decrease and the pharmacologically active free concentration may increase, even to toxic levels.

Results:

There was an association between dosage increase of VPA, total VPA blood levels (68mg/l, reference 40-120mg/l), the concentration of the unbound VPA (37.5mg/l, reference 4-12mg/l) and cognitive impairment (MMSE 20/30; MoCA 15/30) increasing to reversible severe cognitive impairment comparable to a Global Deterioration Scale (GDS) of 6. Six weeks after dechallenge of VPA her cognitive and conative functioning recovered to pre-VPA levels (MMSE 27/30, MoCA 27/30, GDS 1).

Conclusions:

In standard therapeutic drug monitoring, total VPA concentrations are generally measured instead of unbound VPA concentrations due to analytical difficulties, a lack of established reference ranges and (inter)national guidelines not requiring the measurement of free fractions. This case points out that hypoalbuminemia demands regular monitoring of the free concentration of VPA to prevent unnecessary side effects and toxicity. We recommend measuring albumin during VPA use particularly in patients at risk of hypoalbuminemia; including those with nephrotic syndrome, liver disease or older adults.

6.1 Introduction

Valproic acid (VPA) is highly protein bound in blood (80-95%), mainly to albumin (Greenblatt, Sellers and Koch-Weser, 1982; Dasgupta, 2007). Binding of VPA to albumin is non-linear, concentration-dependent and saturable. The unbound VPA concentration can therefore rise substantially with a dosage increase, or if the number of binding sites for VPA decreases (Greenblatt, Sellers and Koch-Weser, 1982; Dasgupta, 2007). In hypoalbuminemic patients, VPA binding may decrease, in which case a patient can experience toxic effects although the total concentration is within the therapeutic range, since it is the free concentration that is pharmacologically active and correlates best with brain concentrations (1). It is then clinically relevant to measure the free concentration of VPA (Greenblatt, Sellers and Koch-Weser, 1982; De Maat, Van Leeuwen and Edelbroek, 2011; Jansen *et al.*, 2012). In clinical practice, total VPA serum concentrations (tVPAc) are generally measured instead of free concentrations due to analytical difficulties, a lack of an established reference range and guidelines not requiring the measurement of free concentration (Greenblatt, Sellers and Koch-Weser, 1982; Dasgupta, 2007; Dols *et al.*, 2016).

6.2 Case presentation

We present a 66-year old woman with bipolar disorder since 2001 who developed severe reversible cognitive impairment associated with a high free concentration of VPA probably due to hypoalbuminemia. She had no comorbidities, was living independently, had no history of alcohol abuse and recently stopped smoking. She had been stable on citalopram and lithium therapy for fifteen years managed by her general practitioner without cognitive complaints. Due to a lithium encephalopathy (3.1 mmol/L), she was admitted to the internal medicines department which led to the decision to stop lithium and subsequently citalopram. Secondly, a nephrotic syndrome was diagnosed and a renal biopsy showed Anti-Phospholipase A2 Receptor (anti-PLA2R) membranous nephropathy which may have caused the lithium intoxication and proteinuria (14g/10 mmol creatinine) with hypoalbuminemia. Prednisone and cyclophosphamide were prescribed to treat the proteinuria. A month after discharge she became hypomanic. VPA 300mg/day was initiated (day 1) as she refused lithium reintroduction and was referred to a psychiatric outpatient clinic. No cognitive impairment was present at referral (day 13), with a Montreal Cognitive Assessment (MoCA) score of 24/30 during hypomania (Nasreddine *et al.*, 2005). After VPA initiation, blood test results (day 18) (supplemental file) were unremarkable besides a tVPAc of 21 mg/l (40 - 120), erythrocyte sedimentation rate of 108 mm/h (1 - 12), glomerular filtration rate of (GFR) 53 ml/min/1.73m2 (>90), and albumin of 23g/l (35 – 55). The tVPAc was determined with an immuno-assay technique (Siemens, Dimension EXL200). VPA was

gradually increased to the maximum of the recommended dose range of 2500mg/day, still resulting in a low tVPAc of 30 mg/l as shown in Figure 1 (day 49). Liver function tests were all within reference range (supplemental file) and there were no drug interactions that could induce a low tVPAc. The patient shifted from hypomania towards mania. To treat the mania, lithium reintroduction was attempted alongside VPA. Reintroduction failed twice as a result of concurrent deliria due to an infection (day 66) and urinary retention (day 70). As her mania worsened during subtherapeutic tVPAc and while awaiting planned admission to a psych-med-unit for lithium reintroduction, VPA was increased to 4000mg/day (day 77) exceeding the maximum approved dose of 60 mg/kg/day by 700mg. The VPA dose increase resulted in a tVPAc of 59 mg/l (day 81). Upon admission she exhibited cognitive dysfunctions (day 88). She was disorientated; answering questions sometimes inadequately or only tangentially and was not structurable. Besides her mania, considered causes included the recent alleged lithium intoxications or a post-delirium state. Based on clinical symptoms she had moderate cognitive impairment comparable to Global Deterioration Scale (GDS) 4 (Reisberg *et al.*, 1982). Lithium 400mg/day was reintroduced (day 90) and increased to 800mg/day after one week. Two days thereafter, she clinically worsened with hypotension, disorientation and somnolence. Due to the severity of her symptoms, she was transferred to the internal medicine department (day 98).Cyclophosphamide was stopped due to a pancytopenia. A lithium level of 1.3 mmol/l led to the decision to halt the lithium reintroduction (day 99). Her MoCA had declined to 15/30 and Mini-Mental State Examination (MMSE) was 20/30 (day 109). Her cognitive function further deteriorated to severe cognitive impairment (GDS 5) following lithium cessation. A CT scan revealed no evidence of cerebral pathology besides mild atrophy. As a precaution, VPA 4000mg/day (tVPAc 68 mg/l) was reduced to 3000mg/day (day 118) below the maximum dose of 60 mg/kg/day. The free concentration of the 3000mg VPA as well as that of the previous 4000mg blood sample was extracted by ultrafiltration, using centrifugation at 1000-2000g at 25C as the driving force for the ultrafiltration. The free VPA in the ultra filtrate was measured by an immuno-assay technique (Abbott ARCHITECT). Albumin had dropped to 14g/L (day 124). In the meantime, the patient severely deteriorated with conative function deficits and activities of daily living dependency (GDS 6). She became apathetic, could barely be motivated to eat or drink and was in need of a wheelchair. She lost the motivation to continue living, spending most of her time in the fetal position. VPA was stopped immediately (day 126) after the laboratory result of the VPA 3000mg/day indicated a free fraction of 66%, with a free concentration of 15.8 mg/l (reference range 4 - 12mg/l) (Sriboonruang *et al.*, 2011), and tVPAc of 24 mg/l. The sample of VPA 4000mg/day of day 113, which was determined retrospectively, showed a toxic unbound VPA concentration of 37.8 mg/l, with a tVPAc of 68mg/l (free fraction 56%). After VPA withdrawal, she switched to a hyperactive delirium and suffered a seizure (day 130). Olanzapine 5mg was started

and she regained conative, cognitive, affective, and physical functioning within days with independency in Activities of Daily Living (ADL). On day 154 she was transferred to the psych-med-unit for further recovery in Instrumental Activities of Daily Living (IADL). Liver function test results were within reference ranges, except for a gamma-glutamyltransferase (GGT) of 58 U/l and alkaline phosphatase (ALP) of 127 U/l. Her cognitive and conative functioning recovered to pre-VPA levels (MMSE 27/30, MoCA 27/30, GDS 1). Discharge followed 197 days after introducing VPA. Later that year lithium was reintroduced without problems.

6.3 Discussion

The cognitive impairment that started just days before admission to the psych-med unit was thought to be partially related to age, manic state, neurodegenerative, lithium intoxications and due to a recent delirium. Change of health care professional contributed to the misinterpretation of cognitive side-effects, as her baseline MoCA score was not transferred from the outpatient clinic. Lithium was thought to be associated to the cognitive decline, due to cognitive complaints during the first and second reintroduction, although there were concurrent deliria and a dosage increase of VPA to 4000mg. Reintroduction of lithium (up to 1.2 mmol/l) following dechallenge of VPA did not result in cognitive impairment. The cognitive impairment could be categorized as a definite adverse event of VPA (Naranjo score 9) (Naranjo *et al.*, 1981). VPA was at first neglected as a causal factor, since the tVPAc was below or within the therapeutic range. However, the eventually detected free concentrations of VPA were far above the reference range and are likely to have caused the severe reversible cognitive impairment. The patient's hypoalbuminemia explains the remarkably high free fraction of VPA and was most likely caused by the PLA2R membranous nephropathy. There was a time-correlation with the tVPAc, free concentration and the severity of cognitive impairment (Figure 1). The cognitive impairment started after a dosage increase of VPA to 4000mg. Her albumin levels dropped starting day 96 from a low but stable 23- 26 g/l to 14 g/l on day 124 which could explain why the clinical condition deteriorated dramatically. We presume the free concentration could have net increased more due to decreased albumin despite the lowering of the dosage. Dechallenge of VPA gradually resulted in a continuous revitalization.

Previous cases have reported VPA related dementia and cognitive impairment, even after long-term use (Evans, Shinar and Yaari, 2011). Cognitive and conative side effects are known to arise in VPA treatment, although very rarely as severely as seen in our patient. A difficulty is that these features, along with other known side effects such as decreased appetite, apathy, aggression, and hyperactivity, can be symptoms of the diseases VPA is given for, particularly bipolar depression and mania. These adverse effects may be misinterpreted, especially when they are less pronounced, progress over time and with advancing age. It

becomes all the more difficult to recognize VPA as the cause of these symptoms when total blood VPA serum levels are within the reference range. Particularly in the elderly there is a risk of underestimation of the free fraction (Sajatovic, Madhusoodanan and Coconcea, 2005; Ng *et al.*, 2009). There is evidence that the VPA affinity for serum proteins decreases with age and age is positively correlated with the free fraction (Kodama *et al.*, 2002). The need for monitoring of the free concentration of VPA is suggested by multiple other case reports (De Maat, Van Leeuwen and Edelbroek, 2011; Jansen *et al.*, 2012). Other cases have been published on VPA-induced encephalopathy due to hyperammonemia (Dealberto, 2007). In our case, ammonia (NH4) was not measured, it is therefore unclear if ammonia could have contributed to the symptoms. Development of hyperammonaemic encephalopathy is unrelated to VPA dose, serum level or severity of hyperammonaemia (Ng *et al.*, 2009).

6.4 Conclusion

As pointed out, due to the pharmacokinetics of VPA, patients with therapeutic total blood levels can have a high free concentration of VPA (Wallenburg *et al.*, 2017) which can therefore be an undetected cause of side effects or even toxicity. This is more likely in hypoalbuminemic patients. We recommend measuring albumin during VPA use if free concentration VPA monitoring is not standard; particularly in patients at risk of hypoalbuminemia (Wallenburg *et al.*, 2017), including those with nephrotic syndrome (Wallenburg *et al.*, 2017), liver disease (Dasgupta, 2007; Wallenburg *et al.*, 2017) or older adults (Sajatovic, Madhusoodanan and Coconcea, 2005; Ng *et al.*, 2009; Wallenburg *et al.*, 2017). This case report suggests that it is necessary to monitor the free concentration of VPA in hypoalbuminemic patients to prevent misinterpretation of side effects or toxicity.

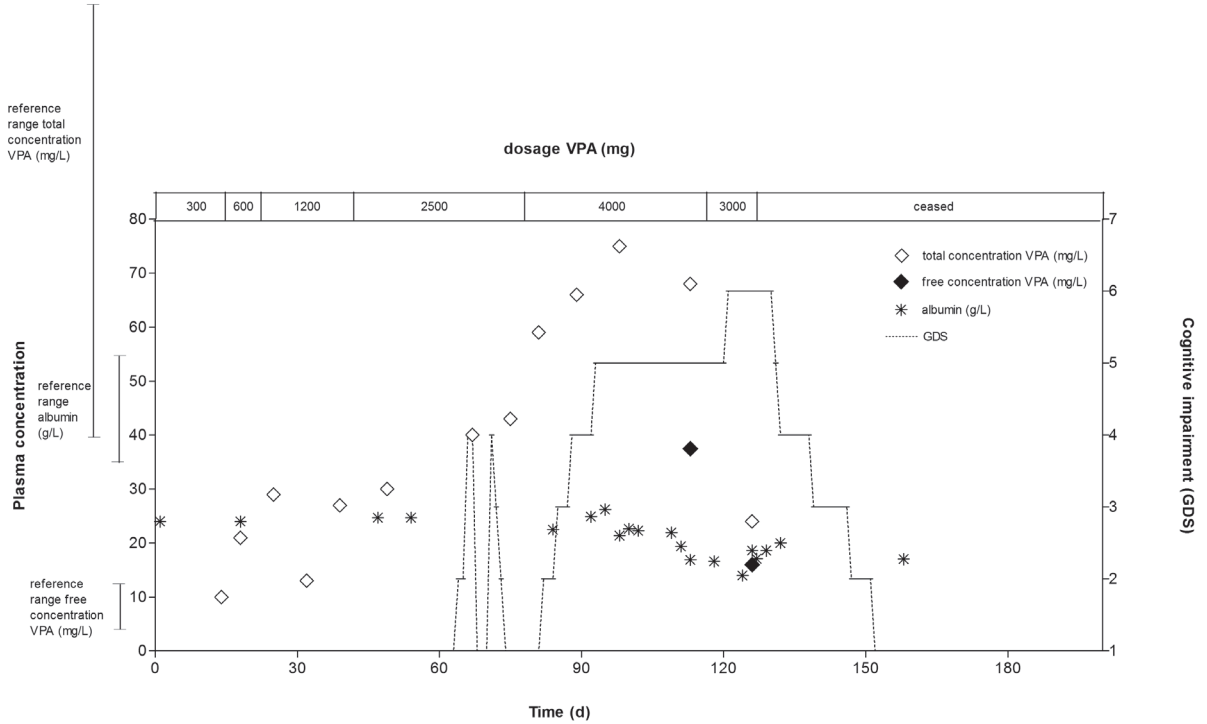

Figure 1: VPA dosage, total and free VPA plasma concentration, albumin concentration and cognitive impairment. VPA dosage is increased to 4000mg resulting in (sub)therapeutic total VPA concentrations after which cognitive impairment becomes visible.

Albumin levels are continuously below the reference range with a drop around day 120. Free concentration of VPA is measured on day 113 and 126; both values are far above the reference range. While the total VPA concentrations were (sub)therapeutic, the free concentrations were toxic.

On day 66 and day 70 a decline in cognitive function can be seen due to the concurrent deliria due to infection and urinary retention.

Cognitive impairment was not measured continuously but by interval with the MoCA at that time, and determined afterwards on a Global Deterioration Scale. Cognitive impairment: 1 = No Cognitive Decline, 2 = Very Mild Cognitive Decline, 3 = Mild Cognitive Decline, 4 = Moderate Cognitive Decline, 5 = Moderate Severe Cognitive Decline, 6 = Severe Cognitive Decline, 7 = Very Severe Cognitive Decline.

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Days	after start VPA					1	15	18	21	25	32	39	42	47	49	54
Date	month	OCT	OCT	OCT	OCT	NOV	DEC	DEC	DEC	DEC	DEC	JAN	JAN	JAN	JAN	JAN
	day	1	14	17	26	27	11	14	17	21	28	4	7	12	14	19
MEDICATION																
Lithium (Li)	mg	1200	1200	0	0	0	0	0	0	0	0	0	0	0	0	0
Li Serum levels	mmol/L	0.8	3.1													
Valproic Acid (VPA)	mg	0	0	0	0	300	600	600	1200	1200	1200	1200	2500	2500	2500	2500
VPA Serum levels	mg/L							21		29	13	27			30	
VPA Free concentration	mg/L															
Citalopram	mg	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0
Olanzapine	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Furosemide	mg	0	0	0	0	0	0	0	40	40	40	40	40	40	40	40
Prednisone	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cyclophosphamide	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lisinopril	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LABORATORY	BLOOD LEVELS															
Glomerular filtration rate (GFR)	ml/min/1.73m2		63		74			53						40		
Creatinine (creat)	umol/l		83		73			92						124		124
Urea	mmol/l		5.4		4.4											
Albumin (Alb)	g/L		24		26.2			23						24.7		24.7
Hemoglobin (Hb)	mmol/L		8.7		6.5			6.8						6.3		
Sodium (Na)	mmol/L		141		147			144						142		
Potassium (K)	mmol/L		4.3		4.1									3.9		
C-reactive protein (CRP)	mg/L mm/h		12		26											
Total Protein	g/L		11.8											5.81		
Total Protein/Creatinine ratio	g/mmolKr		1.19											1.49		
Aspartate transaminase (AST)	U/L		19													
Alanine transaminase (ALT)	U/L		13													
Lactate dehydrogenase (LD)	U/L		192													
Alkaline phosphatase (ALP)	U/L		129													
Gamma-glutamyltransferase (yGT)	U/L		17													
AFFECTIVE MOOD FUNCTIONING	NIMH-LifeChart	0	0	0	0	3	3	3	3	3	3	3	3	3	3	3
COGNITIVE FUNCTIONING	GDS	1	5	4	1	1	1	1	1	1	1	1	1	1	1	1
Delirium	1=still 2=active															
Life events			Admition to an internal ward			Mental health emergency service					VPA 13mg/l, but after 23h by mistake patient					Nephrology
			Stop lithium			Start R./ VPA		Albmicro 2643mg/L urine							MoCA 24/30	
			Stop citalopram					Creat 3.1mmol/L urine								Proteinuria
				Suspected nephrotic syndrom e.c.i.				Ratio alb/creat 849 mg/mmol								

Days	after start VPA	55	63	65	66	67	68	70	71	75	77	81	83	88	89	90
Date	month	JAN	JAN	JAN	JAN	FEB	FEB	FEB	FEB	FEB	FEB	FEB	FEB	FEB	FEB	FEB
	day	20	28	30	31	1	2	4	5	9	11	15	17	22	23	24
MEDICATION																
Lithium (Li)	mg	0	200	200	200	200	200	400	0	0	0	0	0	0	0	400
Li Serum levels	mmol/L					0.3										
Valproic Acid (VPA)	mg	2500	2500	2500	2500	2500	2500	2500	2500	2500	4000	4000	4000	4000	4000	4000
VPA levels	mg/L					40				43		59			66	
VPA Free concentration	mg/L															
Citalopram	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Olanzapine	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Furosemide	mg	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
Prednisone	mg	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Cyclophosphamide	mg	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Lisinopril	mg	0	0	0	0	0	0	0	0	0	0	0	20	20	20	20
LABORATORY	BLOOD LEVELS														CYP	
Glomerular filtration rate (GFR)	ml/min/1.73m2									44	50		58		57	
Creatinine (creat)	umol/l									108	102		89		90	
Urea	mmol/l									17.2			13.1			
Albumin (Alb)	g/L												22.5			
Hemoglobin (Hb)	mmol/L										6.9		6.3		5.5	
Sodium (Na)	mmol/L												136		144	
Potassium (K)	mmol/L												3.6		3.6	
C-reactive protein (CRP)	mg/L mm/h												10			
Total Protein	g/L															1.1
Total Protein/Creatinine ratio	g/mmolKr															0.42
Aspartate transaminase (AST)	U/L												37			
Alanine transaminase (ALT)	U/L												38			
Lactate dehydrogenase (LD)	U/L												378			
Alkaline phosphatase (ALP)	U/L												81			
Gamma-glutamyltransferase (yGT)	U/L												32			
AFFECTIVE MOOD FUNCTIONING	NIMH-LifeChart	3	4	4	4	4	4	4	4	4	4	4	4	4	3	3
COGNITIVE FUNCTIONING	GDS	1	1	2	4	4	1	1	4	1	1	1	2	4	4	4
Delirium	1=still 2=active				1	1			1							
Life events				Emergency room			Start amoxicilline 750mg 3dd1 for 7 days						Poli nephrology: administration due to retention bladder			
		Start prednison			Flu		38.5 C		Lithium stopped. Cognitive impairment due to retention bladder?					Administration Psych- Med-Unit		
								R./ lithium from 200 to 400mg							CYP2C19 IM *2/*17	
			Reintroduction Li												CYP2D6 IM *1/*4	

Days	after start VPA	91	92	93	95	96	97	98	99	100	102	104	109	110	111	113
Date	month	FEB	FEB	FEB	FEB	MAR	MAR	MAR	MAR	MAR	MAR	MAR	MAR	MAR	MAR	MAR
	day	25	26	27	29	1	2	3	4	5	7	9	14	15	16	18
MEDICATION																
Lithium (Li)	mg	400	400	400	400	800	800	800	0	0	0	0	0	0	0	0
Li Serum levels	mmol/L		0.4				1.3	1.2	0.8							
Valproic Acid (VPA)	mg	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000	4000
VPA levels	mg/L							75								68
VPA Free concentration	mg/L															37.5 retrospectively
Citalopram	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Olanzapine	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Furosemide	mg	120	120	80	80	120	160	160	160	160	160	80	80	80	80	80
Prednisone	mg	60	60	60	60	60	60	60	60	60	60	60	60	30	30	30
Cyclophosphamide	mg	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0
Lisinopril	mg	20	20	20	20	20	20	20	0	0	0	0	0	0	0	0
LABORATORY	BLOOD LEVELS															
Glomerular filtration rate (GFR)	ml/min/1.73m2		57	53	54			46		74	76		>90		>90	
Creatinine (creat)	umol/l		90	96	95			110		73	71		58		57	
Urea	mmol/l			13.3				16.7		9.6	10.1		7.9		9	
Albumin (Alb)	g/L		24.9		26.2			21.4		22.6	22.3		21.9		19.4	16.9
Hemoglobin (Hb)	mmol/L				5.6			4.1		7.3	7		5.8		5.6	
Sodium (Na)	mmol/L		148	147	146			146		146	144		142		142	
Potassium (K)	mmol/L		4.2	4	3.6			3.6		4.5	4.6		4.9		5	
C-reactive protein (CRP)	mg/L mm/h				12			18		67						16
Total Protein	g/L										2.92			1.34		
Total Protein/Creatinine ratio	g/mmolKr										0.73			0.54		
Aspartate transaminase (AST)	U/L							53								
Alanine transaminase (ALT)	U/L							59								
Lactate dehydrogenase (LD)	U/L							357								
Alkaline phosphatase (ALP)	U/L							72								
Gamma-glutamyltransferase (yGT)	U/L							34								
AFFECTIVE MOOD FUNCTIONING	NIMH-LifeChart	3	2	2	3	2	2	2	2	2	2	2	2	2	3	3
COGNITIVE FUNCTIONING	GDS	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5
Delirium	1=still 2=active					1	1	1	1							
Life events						R./ lithium to 800mg		Deterioration clinical presentation					MoCA 15/30			
								Hypotension		Fall resulting in fracture of her nose						
									Administration of Packed cells				MMSE 20/30			
								Trasfer to internal ward								

Days	after start VPA	116	117	118	119	121	124	125	126	127	129	130	131	132	133	134
Date	month	MAR	MAR	MAR	MAR	MAR	MAR	MAR	MAR	APR	APR	APR	APR	APR	APR	APR
	day	21	22	23	24	26	29	30	31	1	3	4	5	6	7	8
MEDICATION																
Lithium (Li)	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Li Serum levels	mmol/L															
Valproic Acid (VPA)	mg	4000	4000	3000	3000	3000	3000	3000	3000	0	0	0	0	0	0	0
VPA levels	mg/L								24							
VPA Free concentration	mg/L								15.82							
Citalopram	mg	0	0	0	0	0	0	0	0	0	0	10	10	10	10	10
Olanzapine	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,5
Furosemide	mg	80	80	40	40	40	40	40	40	0	0	0	0	0	0	0
Prednisone	mg	30	30	30	30	30	30	30	30	30	60	60	60	60	60	20
Cyclophosphamide	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lisinopril	mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LABORATORY	BLOOD LEVELS															
Glomerular filtration rate (GFR)	ml/min/1.73m2	>90		61			53		>90	>90				>90		
Creatinine (creat)	umol/l	51		85			96		58	46				42		
Urea	mmol/l	7.3		12.2			17.8		11.2	8.2				6.5		
Albumin (Alb)	g/L			16.6			14		18.6	17.1	18.6			20		
Hemoglobin (Hb)	mmol/L			5.2			4.4		5.2	4.6				4.3	3.9	
Sodium (Na)	mmol/L			139			139		149	148				154		
Potassium (K)	mmol/L			3.2			3.4		3.8	2.8				3.7		
C-reactive protein (CRP)	mg/L mm/h			28			82		86	52			12		15	
Total Protein	g/L			0.59			0.39									
Total Protein/Creatinine ratio	g/mmolKr			0.09			0.08									
Aspartate transaminase (AST)	U/L															
Alanine transaminase (ALT)	U/L															
Lactate dehydrogenase (LD)	U/L															
Alkaline phosphatase (ALP)	U/L															
Gamma-glutamyltransferase (yGT)	U/L															
AFFECTIVE MOOD FUNCTIONING	NIMH-LifeChart	3	3	3	3	4	4	4	4	4	4	4	4	3	3	3
COGNITIVE FUNCTIONING	GDS	5	5	5	5	6	6	6	6	6	6	6	5	4	4	4
Delirium	1=still 2=active					1	1	1	1	2	2	2				
Life events			Redetermination of free VPA 68/37.8 mg/l							Sudden shift from hypoactive delirium to hyperactive delirium.						
			Rhinoplasty under light anaesthesia					Stop VPA	Free VPA 15.8mg/l				(pseudo-) epileptic seizure			
				VPA dose reduction		Patient could not eat or drink by herself. She did not want to continue living, spending most of her time in fetal position.										
					Visit by author: patient severely deteriorated				Transfer to internal ward						Administration of Packed cells	

Days	after start VPA	139	140	144	145	146	152	154	158	165	176	197	215	248
Date	month	APR	APR	APR	APR	APR	APR	APR	MAY	MAY	MAY	JUNE	JUNE	JULY
	day	13	14	18	19	20	26	28	2	9	20	10	28	31
MEDICATION														
Lithium (Li)	mg	0	0	0	0	0	0	0	0	0	0	0	300	600
Li Serum levels	mmol/L												0.4	0.6
Valproic Acid (VPA)	mg	0	0	0	0	0	0	0	0	0	0	0	0	0
VPA levels	mg/L													
VPA Free concentration	mg/L													
Citalopram	mg	10	10	10	10	10	10	10	10	10	10	20	20	20
Olanzapine	mg	5	5	5	5	5	5	5	5	5	5	5	5	5
Furosemide	mg	160	80	0	0	0	0	0	0	0	0	0	0	0
Prednisone	mg	20	20	20	20	20	20	20	20	20	20	0	0	0
Cyclophosphamide	mg	0	0	0	0	0	0	0	0	0	0	0	0	0
Lisinopril	mg	0	0	0	0	0	0	0	0	0	0	0	0	0
LABORATORY	BLOOD LEVELS													
Glomerular filtration rate (GFR)	ml/min/1.73m2				>90				121		>90			81
Creatinine (creat)	umol/l				45				45		45			67
Urea	mmol/l				3.2						4.8			4.8
Albumin (Alb)	g/L								17					37.2
Hemoglobin (Hb)	mmol/L			6.1			6.7		6.6		7			9.4
Sodium (Na)	mmol/L				146				142		138			
Potassium (K)	mmol/L				4.4				3.8		5.8			
C-reactive protein (CRP)	mg/L mm/h													
Total Protein	g/L					0.9					1.03			0.26
Total Protein/Creatinine ratio	g/mmolKr					0.29					0.36			0.15
Aspartate transaminase (AST)	U/L								31					
Alanine transaminase (ALT)	U/L								25					
Lactate dehydrogenase (LD)	U/L													
Alkaline phosphatase (ALP)	U/L								127					
Gamma-glutamyltransferase (yGT)	U/L								58					
AFFECTIVE MOOD FUNCTIONING	NIMH-LifeChart	3	3	3	2	2	2	2	0.5	0.5	0.5	0.5		
COGNITIVE FUNCTIONING	GDS	3	3	3	3	3	1	1	1	1	1	1		
Delirium	1=still 2=active													
Life events								Transfer to old age psychiatry ward				Discharge old age psychiatry ward		
			Suddenly reacting to visitors					No cognitive complaints at intake interview					Reintroduction lithium	
										MMSE 27/30				MoCA 27/30


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CHAPTER

Summary of the main findings and general discusion

7

7.1 Summary of the aims and main findings:

- 7.1.1 Background and aim of this dissertation
- 7.1.2 Section A: Unseen needs
- 7.1.3 Section B: The MoCA validation in different old age settings
- 7.1.4 Section C: The MoCA in clinical practice

7.2 Methodological reflections:

- 7.2.1 Section A: Unseen needs
- 7.2.2 Section B and C: MoCA

7.3 Considerations:

- 7.3.1 Section A: Unseen needs
- 7.3.2 Section B: MoCA validation in different old age settings
- 7.3.3 Section C: The MoCA in clinical practice
- 7.3.4 Implications for clinical practice and health policy, and recommendations for future scientific research
- 7.3.5 The Wilson and Jungner criteria

7.4 Concluding remarks:

7.1 Summary of the aims and the main findings

7.1.1 Background and aim of this dissertation

In clinical practice two seemingly distinct disorder clusters are referred to the old age psychiatry; psychiatric disorders that often manifest themselves by disturbances in 'behaviour, mood or thoughts' and neurodegenerative disorders that often present with decline in 'cognition'. However, there is an increase in the comorbidity of cognitive disorders with age (Ferri *et al.*, 2005) in addition to impaired cognitions related to affective and psychotic disorders (Schouws *et al.*, 2012; American Psychiatric Association, 2013; Baune and Renger, 2014; Bora and Pantelis, 2015). Affective and psychotic symptoms are also common in different dementias (Lyketsos *et al.*, 2002; American Psychiatric Association, 2013; Nederlandse Vereniging voor Klinische Geriatrie, 2014; Eikelboom *et al.*, 2021). Often, prodromal symptoms present with the 'opposite' cluster of symptoms, for example, cognitive problems amongst schizophrenic patients or depression preceding neurodegenerative diseases. This further complicates the diagnosis because of overlapping symptom presentation.

It is estimated that the number of people (24 million in 2018) with dementia worldwide will double every 20 years, reaching 115 million by 2050 (Alzheimer's Disease International, 2018). For the group with mild cognitive symptoms, these numbers were several times higher. In addition, today's patient goes to a physician to request exclusion or confirmation of an underlying substrate as an explanation with increasingly milder cognitive complaints than was previously the case (Grimmer *et al.*, 2015). This, besides the above mentioned co-existing of the symptoms, makes determining an aetiology more difficult (Mitchell, 2009) as both psychiatric and neurodegenerative causes can start with (mild) cognitive deficits. An elaborate neuropsychological assessment is part of the gold standard for identifying the cause.

The patient populations to be examined will grow substantially, and the pressure on waiting lists for comprehensive cognitive assessment will further increase (Alzheimer's Disease International, 2018). Besides as it is expensive, scarce, time-consuming, and burdensome for the patient to do this in specialised outpatient clinics by means of an extensive cognitive examination, a triaging test before a referral is made is desirable. This bedside short test that can help differentiate and objectify whether the patient in question has age-appropriate symptoms, or whether the symptoms fit a (non-neurodegenerative) psychiatric diagnosis, which can be accompanied by subjective or minor cognitive impairment, or that more research may need to be conducted in relation

to (mild) cognitive impairment (Davis *et al.*, 2013; Prince and Comas-Herrera, 2016). This test should then meet the requirements of a short acquisition time, test multiple cognitive domains, and have good sensitivity and specificity for not only dementia but also Mild Cognitive Impairment (MCI) in particular, due to the above-mentioned reasons, among others.

The Mini-Mental State Examination (MMSE) is the most commonly used test to quickly detect cognitive impairment (Folstein, Folstein and McHugh, 1975). However, the problem with MMSE is that it easily scores false negatives in mild to moderate cognitive impairment (Nasreddine *et al.*, 2005; Davis *et al.*, 2013). If someone experiences symptoms but makes the MMSE adequate, it does not exclude (mild to moderate) cognitive disorders. Thus, the MMSE seems inappropriate as a precise screening instrument for mild-to-moderate cognitive complaints or patients with complaints who have a background of a higher level of education (Nasreddine *et al.*, 2005). A fast test with discriminatory power in this group of patients with a non-uniform presentation is of great value. The Montreal Cognitive Assessment (MoCA) is a short screening test (10 minutes long) for cognitive complaints and is designed for this purpose (Nasreddine *et al.*, 2005). In doing so, the MoCA seems more appropriate for finding mild to moderate cognitive impairment, which the MMSE does not adequately detect (Nasreddine *et al.*, 2005; Davis *et al.*, 2013). The test has already been validated in over 27 languages (*mocatest.org*), with good sensitivity and specificity of 90% and 87% for English and French, respectively.

However, the results of the Dutch version in patients with cognitive symptoms in a geriatrics department deviated from this for unknown reasons, with a sensitivity and specificity of 72% and 73% for MCI, respectively, compared with healthy controls (Thissen *et al.*, 2010). Validation has also been performed in several specific populations, including those with vascular dementia (Ihara *et al.*, 2013) and frontotemporal dementia (Freitas *et al.*, 2012). It is clear that the test should be validated in specific populations to maintain high reliability (Rossetti *et al.*, 2011).

Depending on the population in which the test is administered, reliability changes. The positive predictive value (PPV) decreases and the negative predictive value (NPV) increases when there are fewer cognitive impairment patients in the studied population. For example, for the MMSE in a memory clinic, the PPV is 86% and NPV is 73%, and in general practice, PPV is 54% and NPV is 96% (Mitchell, 2009).

The above underpins the fact that an increasing number of people have dementia; they are examined earlier in the process, and this interferes with regular (psychiatric) treatments

and complicates diagnostics due to increasing overlapping symptom presentation. A validated short test that allows the scores to be interpreted properly can help identify or exclude (mild) cognitive impairment. The MoCA is becoming the 'test to be used' for short cognitive screening tests, rather than the MMSE to identify mild cognitive impairment (MCI). Internationally, the MoCA has been well validated in different settings; however, in an (old age) psychiatric setting so far no validation study has taken place'.

In addition to the preceding summary of arguments for introducing an objective cognitive test, there is also the following. One must consider that patients tend not to mention all of their needs during visits. The symptoms experienced do not always have to correspond to their objective symptoms. This also applies for what close relatives report. This is true not only for cognitive impairment but also for other needs in old age psychiatry. Hence, many health problems remain unresolved. Disagreement on the *needs* and the needs that need to be met can result in unnecessarily lower quality of treatment (Stobbe *et al.*, 2013) and avoidable lower compliance (Hancock *et al.*, 2003). The ability to tailor treatment will enhance the outcome. Therefore, we must be aware of and consider that patients are not always able to properly articulate or draw attention to their request for help or, in fact, the cause of their complaints. This may be because, for example, they are ashamed of, in denial of, or do not understand the cause of their complaint (i.e. patient delay) or because, for example, they cannot articulate it well, the doctor does not understand it properly, and/or initiates the necessary or supportive examination too late (i.e. doctor delay). The CANE is designed to be used in old age psychiatry to identify a wider area of needs among the elderly, which have not yet been met. It uses not only the perspective of the doctor but also the perspective of the patient and, if available, of the next of kin.

Summary of the Aims

Section A:

What is the patient's (unseen and unmet) need for help in old age psychiatry according to the CANE? How do these factors relate to patient characteristics? Are they different from a setting comprising younger patients? We conducted this study specifically in a population of older patients with bipolar disorder, as older bipolar patients tend to be more complex, with more cognitive decline among other complications than their younger counterparts (Schouws *et al.*, 2012; Dols *et al.*, 2014).

Section B:

Validating the MoCA in an old age psychiatry setting. Is the MoCA reliable for distinguishing MCI from dementia and from those without cognitive problems (especially when all of them are referred to an old age psychiatry setting)?. Would the MoCA be suitable as a screener in old age psychiatry?

Is the MoCA able to discriminate in a memory clinic setting where the entire tested population is suspected of having cognitive disorders? Can the MoCA be used as a triaging test in a memory clinic?

Section C:

How to use and improve the MoCA in clinical practice? Can the MoCA, with a double threshold, help improve its use in old age psychiatry for patients with a subthreshold state?

7.1.2 Main findings of Section A: Unseen needs

The aim was to gain insight into the needs and unmet needs of patients in old age psychiatry, particularly those with bipolar disorder. For this purpose, we used data collected from patients with bipolar disorder aged older than 60. The numbers of '*needs*' were examined and how many of these were '*unmet*' was determined. The relationships between different patient characteristics were also examined. It was hypothesised that patients with higher numbers of '*needs*', whether met or not, would have a poorer outcome on the parameters of general functioning, mood, cognitive functioning, IADL, quality of life, and social cohesion. These different parameters were measured with appropriate instruments such as the GAF, CES-D, YMRS, MMSE, GARS, MANSA, and the number of contacts that the patient maintained.

The results of our study with respect to bipolar elderly patients, as described in Chapter 2, showed that the mean number of '*Total Needs*' 4.31 (SD 3.48) reported by patients corresponded to the number scored by the clinicians (4.4 SD 3.56). This showed that most needs occurred in the areas of physical health, housing skills, and mediation. This is in line with the literature on older patients and their needs, which were scored using the CANE (Walters *et al.*, 2000; Arvidsson, 2001; Hancock *et al.*, 2003; Meesters *et al.*, 2013) and also with our expectations. This was also reflected in the fact that the practitioners also recognised these needs as the most common, and that they had also largely been accounted for. The number of total mean '*Met Needs*' scored by the patients and the therapists differed little, 3.50 (SD 2.81) versus 3.95 (SD 3.18) and should be regarded as not significant.

As far as unmet needs are concerned, a different picture can be seen in the research. Here, the patients score a much higher number in the relative sense; 0.81 vs 0.49. Although this is a small difference in the absolute sense, it is of great significance. The practitioners underestimated (compared to the patients) the mean number of unmet needs, whereby one out of five reported needs according to the patients had not been met for all domains combined. Therefore, there is a large discrepancy in reporting unmet needs between patients and practitioners, especially in the psychological and social domains, resulting in nearly one out of the three needs not being met in the latter according to the patients. The other domains were scored equally between patients and practitioners. This was also reflected in the Cohen's Kappa coefficients, a statistical measure of agreement between the staff and the patients, in which all high agreement ratings (good and very good agreement expressed in kappa values of 0.61-0.80 and higher) occurred in the environmental and physical domains, but in which almost all items belonging to the social or psychological domains had a low agreement ($\kappa < 0.40$) between the ratings of patients and practitioners. At the item level, the lowest per cent agreement between patients and practitioners was on the items of company, medication, and physical health.

As for memory, the staff scores more needs than the patients for met needs, but less for unmet needs. These results seem to be in line with the expectations that patients tend to report fewer memory complaints.

In relation to patient characteristics and correlations with the number of needs, our study found that most of the clinical variables, measured: age, MMSE GAFp, CES-D, and YMRS, show a correlation only with the total needs and not with unmet needs scored by patients or their staff. However, there are exceptions to this 'rule'. The staff rating of total needs only correlated with depressive symptoms (CES-D) and not with mania symptoms (YMRS). Age showed only a correlation with total needs as scored by the staff, and not when rated by patients. As for the correlation with unmet needs, all, besides GAF and patient rating, show no significant correlation. Therefore, if we consider the above findings' clinical characteristics, we see a tendency that most of these characteristics are recognised by staff and patients to influence the number of total needs, but they are accounted for as there is no correlation with unmet needs. In contrast, the network size, social participation, and quality of life (MANSA), summarised as social variables, tend to have a significant negative correlation with total needs as well as the number of unmet needs. Network size is the exception for unmet needs, according to the staff. This could be explained by the need for these variables not having been accounted for.

7.1.3 Main findings of Section B: The MoCA validation in different old age psychiatry settings

The results are described in detail in Chapters 3 and 4. First, if we compare our data with the (original) literature, using healthy controls as the reference group, excellent accuracy was found in our study, corresponding to the results described in the original study and other studies with a case-control design (*mocatest.org*; Davis *et al.*, 2013; O'Caoimh, Timmons and Molloy, 2016; Carson, Leach and Murphy, 2018). At the cut-off based on the original study (MoCA<26), the sensitivity and specificity are high (95%) and good (73%), and it is comparable to the original study and many other studies with healthy volunteers as control subjects. For the more likely situation of determining whether the MoCA can be discriminatory among all referred patients to geriatric psychiatry who have and do not have cognitive impairment, the results are less favourable than in the originally reported study and case-control studies. The area under the curve (AUC) drops from excellent accuracy (0.93) to a fair to good accuracy (0.77) (Fischer, Bachmann and Jaeschke, 2003). Logically, the sensitivity remains the same and is excellent (> 95%). However, the specificity drops significantly to a questionable level to even below 40% at a cut-off of <26. If we further narrow down or concentrate the population to only referred patients in whom a cognitive disorder is suspected after baseline assessment, the patient groups to be analysed may increasingly resemble each other and it will become increasingly difficult for a test to distinguish the different aetiologies in this group. Again, the total MoCA scores were significantly different between the different study groups and were similar to those in the literature and our study on all referred patients. The AUC remained good, and the specificity remained similar for all referred patients and of moderate level; 47% at MoCA <26, rising to 73% at a MoCA score of <21. With these results, we conclude that of all the referred patients with MCI and mild dementia 95% have a MoCA of <26 (sensitivity), which is meaningful for clinical practice. The optimal cut-off values for dementia are <21 and for MCI <26. When a patient in the total referred patient group, that is, screening, has a negative MoCA (meaning a value of ≥ 21), it can be stated with 98% certainty that this person has no dementia (NPV). An MCI can be ruled out with 94% (NPV) certainty with a score of 26 or higher in this group (with this prevalence). In the cohort of suspected patients (i.e. triaging), 90% (PPV) of those with an MoCA score of <21 will have cognitive impairment (MD+MCI), while 94% (NPV) with an MoCA score of ≥ 21 will not have dementia. This allows for a significant reduction (50%) in referrals in old-age psychiatric care through the MoCA by selecting those who do not need further referral to a memory clinic, even if they were suspected of cognitive impairment after the initial assessment. The PPV was too low for both situations to confirm a diagnosis (both MD and MCI) using only a MoCA in an old-age psychiatric setting.

7.1.4 Main findings of Section C: The MoCA in clinical practice

Chapters 5 and 6 discuss the outcomes of the use of the MoCA in clinical practice. In Chapter 5, we substantiate why and which two cut-off values can best be used, what the consequences could or should be, and why, when using the MoCA with two instead of one cut-off value. We compared different selection methods to determine who is and is not (yet) a candidate for a more extensive follow-up study for cognitive problems. The optimal strategy found among the compared strategies was to use the MoCA to select, after a history interview, those patients who were suspected of having cognitive impairment in whom an elaborate follow-up examination is promptly desirable (MoCA <21) and in whom this comprehensive examination is very likely to show no cognitive decline (MoCA ≥26); therefore, a further referral is not desired. The use of one cut-off point also does injustice to the continuum of cognitive impairment where the two extremes, dementia on one side of the spectrum and no cognitive impairment on the other end, will result in a state that falls in between, namely, MCI. Using two cut-off points improved many parameters used to assess test efficiency compared to one cut-off point. The accuracy, PPV, and NPV improved, but more importantly, the number of false-positive referrals could be reduced by 65% without adding more false negatives. This is essential, especially in consideration of the future substantial increase in referrals with cognitive symptoms if the diagnostic pathways are not to be overcrowded. Thus, although people often intuitively use the MoCA with an uncertainty range surrounding the one cut-off in clinical practice, resembling, therefore, two cut-off points, our study has now added the scientific rationale and motivation for which two cut-offs are best used. The use of two cut-off points also adds to the value of the MoCA in terms of MCI versus mild dementia. Although both are entitled to good diagnostics, their priorities differ. Thus, especially in situations of scarcity, that is, when determining how money and time can best be spent, an MoCA with a double cut-off point can be helpful. It also provides the possibility to (quickly) categorise patients into three risk groups: -no indications of cognitive impairment, -possible MCI, -high risk of MD, and implementation of different policies. We discuss the suggested policy for MoCA scores that fall between these cut-off values. Instead of choosing between referral and no referral, with the in-between group (MCI) previously falling under one or the other policy, a double cut-off point can also be used to choose a third option: active follow-up without referral for a costly and burdensome examination of an elaborate neurocognitive assessment. As this active monitoring could also be performed using the MoCA. The MoCA has been shown to be appropriate for monitoring cognitive development (Krishnan *et al.*, 2017). With this, not only flexibility and time but also money can be gained up to €1000 per avoided false positive referral.

In Chapter 6, we present a different topic. That topic is so important that we thought it was worth publishing. However, the presented case study stands for more than the clinical topic, as it also stands for the importance of the use of a cognitive screener in old age psychiatry, that is, the MoCA. Our patient was an extreme example of a misjudged intoxication. It did not remain unseen as it was so extreme in the end, but it is quite likely that many others would remain undiagnosed. By not measuring the correct blood concentration of valproic acid, that is, free fraction, unseen side effects can appear, including cognitive impairment. Especially when they start gradually and with increasing age, cognitive side effects are prone to be attributed to the reason why one takes valproic acid, age, or, in the case of more severe impairment, to a neurodegenerative aetiology. Even if one is aware of the side effects of valproic acid, and a blood sample to measure the total valproic acid concentration is taken, the result can be misleading when the free fraction is not known. As is still custom, in Europe, it only reports the total valproic acid concentration instead of the unbound concentration. This was the primary message of this chapter, but a secondary message is as follows. We want to emphasise that the routine use of the MoCA in old age psychiatry can make a difference. Even though the score was high or good at the beginning, without exaggeration, having an initial MoCA score saved the patient's life. If it were not for the first (normal) MoCA score, the lower second MoCA score would have been attributed to the patients' current functioning, including a recent lithium intoxication, and age and alarm bells would have sounded too late as a drop of 9 points on the MoCA would not have been noticed. This case report shows that not only is the MoCA score on indication is of value, but a baseline MoCA is of value as well. Especially in an old age psychiatric setting, due to age, medication, and comorbidity, the patients are at risk of developing cognitive impairment for various reasons now or in the near future.

7.2 Methodological reflections

We want to discuss not only the outcomes and implications of our study but also its limitations. This section focuses on the general methodological limitations of this dissertation. The specific limitations of each chapter are presented in the corresponding chapters.

7.2.1 Methodological reflections of Sections A: Unseen needs

The question that needs to be clarified is whether elderly psychiatric patients differ from their younger equivalents in care needs, in general, and in certain diseases or domains, such as cognitive impairment, in particular. Do they only differ in quantity, that is, are they more of

the same? Alternatively, if so, do they differ in topics or domains, that is, quality? Narrowing this major question down creates opportunities to study the population in more detail. Our research question focused on the care needs of older patients with bipolar disorder. There are several reasons why this group was specifically chosen, including practical considerations. First, little was known about this group in terms of their needs; they are well-defined, and there is evidence that they differ clinically from patients who experience this disease at a younger age. To be able to compare older and younger patients accurately, data that meet certain conditions are needed. An important condition is that the circumstances of the different patient groups being compared are similar. There were no studies for bipolar disorder (yet) using the CANE or CAN(SAS) to make a good comparison to draw conclusions between young and old patients. This is a disadvantage. However, there have been studies on other diseases and care needs of older patients using the CANE. Here, there was a very big advantage in that these studies had been performed under almost the same conditions as our study. That is, the same research group was in the same region. This minimised or neutralised many variables that could otherwise be of significance.

By narrowing the general question down, that is, zooming in, one can see more items in detail, and we were able to obtain information specific to this population. With this, tailoring treatment can be optimised better, which is the main goal of the study. One factor that was not zoomed in on was the subdivision of the various bipolar disorders. Our sample did look at demographics and the DSM-IV subdivision into bipolar I and II disorders. However, no distinction was made between these subtypes or between early- and late-onset. Although our population consisted largely of patients with early-onset bipolar disorder, it is interesting to make this distinction to answer specific questions.

Another noteworthy point is that we did not include the perspective of the next of kin, even though this is a feature of the CANE. This could add an important extra perspective on the patients' needs and is especially interesting in respect of cognitive problems. Unfortunately, most patients did not provide consent to interviewing a family member or informal caregiver.

One concern in the design of this study is that the MMSE was used to assess cognitive functioning. There are justifications as to why the MMSE was chosen, especially for a study conducted in 2012. However, in the context of the entire study, not having used the MoCA for this purpose is a missed opportunity. For this particular study, as discussed earlier, the MoCA would also have an advantage, as it is more sensitive to mild cognitive symptoms. This would also allow us to compare the results of specifically this group of

patients with the cohort of the study on the MoCA. Even though it is a missed opportunity from the perspective of the entire study, as presented in this dissertation, it is not necessarily the case for the individual study presented in Chapter 2. By choosing the MMSE, this specific study could be more accurately compared with the results of its sister studies with a different disease as a subject as well as with other publications. It should also be taken into consideration that at that time, the MoCA was not yet in general use and had not been validated in Dutch. In 2012 when the study was designed, the MMSE was still the 'test to be used' for rapid cognitive testing.

7.2.2 Methodological reflections of Section B and C: MoCA study population

For the study of referred patients to geriatric psychiatry, we wanted to determine the criterion validation of the MoCA for MCI and mild dementia in this population. Although the MoCA has been validated many times, it has not been performed for this specific setting. It also turned out that the many validation studies that had already been conducted for various other settings were not very useful, not only because of the difference in setting, but also because many studies used healthy controls as a control group, that is, not patients but completely symptom-free volunteers. This introduces a case-control bias that can impact the outcome (Davis *et al.*, 2013; Bossuyt *et al.*, 2015), particularly, on the outcome of specificity. By comparing the study group to healthy controls who not only have no disorder under consideration but actually have no (subjective) complaints at all, and thus normally would not be referred for or assessed with a MoCA. Although one may envisage situations when this could occur in practice (e.g. screening the general population or knowing someone's baseline functioning), the clinical reality is that this population will rarely be screened for cognitive symptoms in daily practice. In clinical practice, the test is more likely to be administered in the following settings: a population at higher risk with or without complaints, that is, screening, and a population with (different types of) complaints as well as (multiple) suspicions, that is, triaging. Therefore, the added value of a test is to be able to distinguish, in a group of patients at higher risk with or without subjective complaints, between those with and without objective cognitive complaints. This is better addressed by a cohort study, or, in other words, by assessing everyone from a certain population (with symptoms). Nevertheless, we, too, included a group of healthy volunteers in our study. This was done not only to show the extent of this effect (case-control bias), but also to better compare our results with other studies that chose this case-control design, similar to the original study of the MoCA (Nasreddine *et al.*, 2005).

In addition to 'demonstrating' the methodological shortcomings of other studies, it is important to reflect on the shortcomings of our own study.

The goal of the studies in this section is to validate the MoCA for specific conditions that exist in geriatric psychiatry. Different conditions affect the reliability of a test because the population being tested is different. Of course, the most striking feature here is the advanced age of the referred patients (compared to general psychiatry). Frequent psychiatric complaints as a reason for referral and disorders are also a distinctive feature (versus non-psychiatric settings). In addition, widespread cognitive impairment is a factor that affects outcomes (prevalence). This last fact ensures that even within geriatric psychiatry, the population may also vary, and thus, it depends on the time of testing in the diagnostic process. Whether you test everyone, regardless of the referral reason, or whether you test only patients who are suspected of having cognitive symptoms after the initial interview, affects the population composition and thereby, the accuracy of the test. Therefore, we also examined the MoCA in two common settings or 'the moment of assessment' that occurs in old age psychiatry; in everyone referred to old age psychiatry (screening), or only in a population that was suspected of having cognitive problems (triaging). A methodological consideration was the creation of these two 'different' settings. One could argue that the second setting (triaging) was a simulation of the clinical memory setting. In retrospect, we selected patients who were referred to our memory clinic from the cohort of the first setting using patient records. Nevertheless, we think that this is a valid and efficient method, as the only inclusion criterion added was whether the patient was being referred to our memory clinic. By creating these settings, we attempted to make the study population resemble the clinical reality, but it will never match exactly. The study conditions will be (intentionally) rigidly defined through exclusion and inclusion criteria to clarify who is involved and increase comparability across groups. In addition, this is often used for eliminating other influences, for example, in many studies with the MoCA, psychiatric comorbidity was excluded. Clinical practice, on the contrary, is often fluid. This fact also reveals a limitation of our study.

Pragmatism also plays a role in the choice of cohort study design based on patients record research. If treatment, as usual, was to be deviated from and non-suspect patients had been offered a more extensive assessment, this had to be done on a voluntary basis. This would create two groups: those who participate in this follow-up study and those who do not. In addition, there would be a realistic chance of dropouts. There would also be unintended selection, and thus, a risk of bias. This is not often the case with a cohort design, but this also has disadvantages, including the previously mentioned rigid in- or out-classification by the total MoCA score without nuances. Again, as with using healthy

controls, a matter of consideration should be that we used as a reference group a lot of 'unrealistic' patients, as the majority did not have subjective cognitive complaints. This is true in a sense, but at our old age psychiatry clinic, almost all referred patients will receive a MoCA during the initial interview, as we consider them at risk, now, or in the near future. Therefore, we wanted and needed to know the MoCA's accuracy in this situation.

There is another methodological concern that needs to be addressed that arises from 'not everyone who participated in the study receiving the same diagnostic tests'. This counts for the group that was *not suspected of cognitive impairment* by an old age psychiatrist. If they would receive the same diagnostic test as all other participants, they would receive an extensive follow-up assessment only to confirm the clinical view of no-cognitive impairment. Although this would be important for detecting false negatives by using the gold standard, it was ethically and socially unjustifiable. The cost, in addition to the time investment of patients, would not be proportional, especially because false negatives can also be detected by other means, although with less certainty. This was done by following up on those who were not referred for an extensive neuropsychological examination to determine if cognitive complaints would develop over time. In addition, when in doubt, referrals were made by the practitioners, as is often the case in practice, resulting in a few false negatives after the initial interview.

In the study using the CANE (second chapter), we included the MINI (Sheehan *et al.*, 1998) assessment to standardise the DSM-IV diagnosis. We did not include this in the MoCA study. The main reason for this was that we considered the diagnostic route advised by international criteria as the gold standard.

One of the inclusion, or in fact, exclusion criteria, that may be critically evaluated was the timeframe in which the MoCA had to be taken after the initial interview. We set this to three months (100 days). You want the MoCA to have been conducted in the period in which the other parameters were also collected, such as the diagnosis and the GAF or GDS15 score. Although cognitive impairment is often not assumed to change rapidly, it can do so. Especially in geriatric psychiatry, there are situations in which this is precisely what can occur. One might think of medication or a mania, as the cause of cognitive symptoms. Again, the difference between the study design and clinical practice comes into play. Whereas in clinical practice a cognitive test is often delayed until acute affective or psychotic symptoms have diminished, for this study, one wants them to coincide. Without going into the benefits of whether the decline in MoCA and the primary complaint coincide, it is important to be aware of them. This has implications for the interpretation

of data and its applicability to individual patients. For the study, where everyone was assessed with a MoCA one week after the initial interview, handling a short time frame was important. This is in an attempt to interpret these data with current clinical practice, whereby patients are routinely given a MoCA after the initial interview. For this group, a 3-month timeframe is nearly inappropriate as an inclusion criterion, but for the 'suspected cognitive impairment' group, one can argue that it is not. Barring exceptions, this is especially true for neurodegenerative disorders. In the literature, we often find a limit of 3 months, which, evidently, is not a decisive argument. If we closely consider the timing of the MoCA's assessment relative to the other parameters (determined during the initial interview), we see that the majority had been collected within three weeks in our cohort.

The discussion above argues that the study group should resemble the group for which the test is going to be used. In an idealistic case, this translates to a perfectly matching study subject for each patient. In practice, the best control data are the patient's own baseline data for self-comparison in a study context. Thus, obtaining baseline values for individual patients is important. These data are lacking in our study. A longitudinal study design could provide even more certainty regarding the course of MoCA, with respect to the development of cognitive impairment as well as the influence of comorbidities, such as depression, on MoCA.

Comorbidity is a challenging issue in many studies. By excluding them from your research group, you can create an increasingly uniform group where the results can largely be attributed to the remaining parameters. However, the less diverse or more selected the research group becomes, the less it will resemble the real world. In our cohort, some comorbidities (alcohol, Cerebrovascular accident, and obvious dementia) were excluded, whereas some (psychiatry) were explicitly not excluded. Although we have made a reasoned choice for this, there is also a danger in that it does not approach the clinical reality in which alcohol use, hidden or otherwise, is present. The fact remains that in clinical practice, the examiner (hopefully) assesses not only the MoCA total score but also how it was obtained, incorporating the patient's clinical and demographic data.

7.3 Considerations

7.3.1 Considerations of Section A: Unseen needs

The Camberwell Assessment of Need for the Elderly (CANE) is adapted from the Camberwell Assessment of Need (CAN, which has 22 topics) to suit the specific needs of older adults. It assesses four different domains: environmental, physical, psychological, and social needs, with 24 topics and 2 extra for the carer-giver. The adaptation of the CANE can be found

in typical old age issues like memory, eyesight, mobility and continence, and leaving out 'typical' younger adult issues like dependents (children), drugs, sex, education and digital communications. One can argue that views to replace these latter issues have changed since the CANE was introduced by Reynolds in 2000, as some items can also affect the lives of older patients. These differences must be considered when comparing CAN and CANE results.

The results of our bipolar patient cohort are consistent with those obtained in the literature on older patients using the CANE and showed that the needs reported most by the patients were also reported most by the staff (Walters *et al.*, 2000; Arvidsson, 2001; Hancock *et al.*, 2003; Meesters *et al.*, 2013). Patients are referred to our hospital for health issues and the staff tries to meet their needs. We speculate that caregivers could also observe these needs on a daily basis in their private lives among community-dwelling older adults. It may be a stereotypical thought of older 'dependent' persons having needs in household skills, next to physical health and medication, but it seems there is some truth in it. This could be a reason why the staff (and often next of kin) are aware of these needs and, therefore, also contribute to the fact that these needs are mostly met even though they are often present. This reasoning does not hold true for physical health, and a substantial percentage of needs remain unmet. Again, we can speculate with common sense that with older patients, physical health will deteriorate and hence create more needs. As the CANE scores a need as unmet when a function falls below 'some minimum specified level and if a potentially effective remedy existed'. The latter, particularly for the item 'physical health', is important. However, age does not seem to be a major contributor to needs, especially unmet needs, although this seems counterintuitive. Our study, as well as others, found no correlation between age and unmet needs as scored by patients as well as staff (Lloyd, King and Moore, 2010) and some studies with even older patients (mean age 80 years) reported (50%) fewer needs and unmet needs. Could this be because of the latter criteria stating that a potentially effective remedy should exist for a need to be judged as unmet? It is known that older patients tend to accept burdens as a fact of life. These latter criteria seem to introduce some subjectivity. How and who is to decide if a remedy exists for the physical burden that comes with ageing?

A major finding of this study was that the total number of unmet needs was underestimated by the staff. However, more importantly, most of these poor agreements were in the social domain and, to a lesser extent, in the psychological domain. In absolute numbers, they may seem to be a minor problem, but expressed as a percentage of the reported unmet needs from the patients' view, there is a substantial disagreement on these unmet needs. This seemingly 'blind spot', even though the absolute numbers are low, comes with a chain reaction of consequences and it needs the attention of staff or at least their

awareness of this, given that we found that unmet needs correlate with lower quality of life, poorer social participation according to staff and patients and network size according to the patients. This is in concordance with findings in the literature on unmet needs and reporting impaired quality of life (Field, Walker and Orrell, 2002; Stein *et al.*, 2014), lowering the motivation for treatment (Stobbe *et al.*, 2013), and raising the number of visits to the staff (Goossens *et al.*, 2007). These findings seem to be independent of diagnosis and suggest a key role for social and emotional support (Stein *et al.*, 2014). This was underlined by the findings of our study that company and daytime activities were the most frequently reported unmet needs by both patients and staff. Our study, as well as the literature (Houtjes *et al.*, 2011; Meesters *et al.*, 2013), confirm our hypothesis that patients with more psychiatric symptoms report more needs. Symptoms create needs, but unmet needs can induce symptoms. The starting point in this circle is difficult to distinguish, but it seems that the needs the clinical variables (CES-D, YMRS, GAF, and MMSE) induce are being met, as there are no correlations found with unmet needs. This could be because staff members anticipate the needs that come with more psychiatric symptoms. The more (psychiatric) symptoms one has, the more needs are expected and anticipated. However, this only counts for clinical variables and not social variables (MANSA, network size, social participation, and quality of life). This is in line with the assumption mentioned at the beginning of this paragraph of awareness due to stereotypical thinking and considering social variables not as a core goal of secondary health services. However, the correlations found between the social domains with unmet needs besides total needs also underline the necessity to look beyond the clinical picture of the patient and consider helping with social issues as they affect treatment outcomes and well-being (Valtorta 2012).

Is there, in addition to the stereotypical thought of the dependent elderly, (still) a taboo on addressing social isolation? Even though one could consider these variables not to be the main treatment goal of psychiatry, they will affect psychiatric health and should not be ignored. This is an important lesson, for not only clinicians but also policymakers. Nowadays, treatment should be more than clinical recovery, as social, functional, and personal recovery also have a role in patient health.

7.3.2 Considerations of Section B: The MoCA validation in different old age psychiatry settings

No matter how much we try to approximate clinical practice in a study population, it will never match reality. Even if we are generally aware of this, we should keep this in mind when using the study data in clinical practice. This immediately brings forth another

pitfall. How useful is the proposed theoretical cut-off in practice, especially for cognitive impairment? As much as the MoCA will produce a solid score and thus appear to be an arbiter between cognitive impairment and no impairment, clinical reality, again, involves many other factors that can affect this MoCA score. This is exemplified in our study. The mean MoCA scores differ significantly from each other per cognitive group. However, the range (or SD) is too wide and shows us that the individual score must be weighted with this knowledge. The 'best' mean cut-off as suggested by a study is a mean and does not fit all individuals due to personal demographic and clinical factors. These individual factors range from intoxication, (lack of) motivation, or anxiety to disabilities, such as poor eyesight. The MoCA score itself does not correct for these factors. All of these clinical data must be considered and many will be considered in the clinical reality, but on the other hand, many factors that are (or appear to be) influential may remain unknown and may not be included or even be excluded in a study. This can range from the level or years of attended education (MoCA corrects for this), through alcohol use (corrected by our study) up to literacy and ethnicity of the patient (not corrected in our study, but some US-based studies do). For research, you have to create study groups, and you need to translate these results to individual patients. However, these groups can never fully match the unique patient since the study outcomes are averages of several factors, whereas the individual patient consists of many factors. This is clarified in our study by using education as a factor. Although the MoCA tries to correct this with one extra point for education of 12 years or less to reduce the number of false negatives, it will never be able to offer a custom-made correction. Stratification is sometimes suggested as a solution (Oren *et al.*, 2014; Wong *et al.*, 2015; Borland *et al.*, 2017), but in practice, it seems impractical, given the many parameters that may be affected and need to be stratified. Through years of education (<12; + 1 point), an attempt is made to capture the lower baseline values of an individual patient. However, certain groups do not seem to be corrected well with this, and there are suggestions to use literacy (Sisco *et al.*, 2015). Low baseline values can play a role, as can high baseline values. Thus, in our study, we see that a very high level of education can also lead to false negatives.

Other factors, especially in old age psychiatry, that can greatly influence the MoCA score but seem to differ from individual to individual, are psychiatric diagnoses. This is clearly illustrated in Figures 2a and b of Chapter 4. The mean total MoCA scores are significantly different among the three cognitive groups. If we distinguish more on an aetiological level, a different situation appears, and the use of the MoCA in clinical reality becomes less distinct (sharp). First, Figure 2b confirms that the MoCA score corresponded well with

the clinical view (made without knowledge of the MoCA score) of the psychiatric patients with or without MCI. However, what is very prominent is the wide range of scores per (certain) psychiatric disease; there is a tendency of concluding that you either have or do not have cognitive problems that come with that disease. Personality disorders and 'mixed diagnoses' of non-affective and non-psychotic disorders do not have this tendency. Personality disorders with the highest MoCA score seem to confirm the clinical experience. This seems to correspond with the findings in the literature, where there is heterogeneity among patients with affective and psychotic disorders in the severity of cognitive impairment. Again, some patients can be seriously affected, and others cannot be distinguished from normal controls (Van Rheenen *et al.*, 2020). However, when patients are diagnosed with MCI and depression, they score worse in multiple domains than MCI patients without depression (Ma, 2020). In general, the literature states that unipolar depression seems to affect cognition less than bipolar depression, and the bipolar profile resembles that of schizophrenic patients, although less severe (Van Rheenen *et al.*, 2017).

Our study seems to confirm that objective cognitive problems can often be categorised as MCI. Why some patients with depression and MoCA scores that are normally deemed to have MCI but are not diagnosed with MCI has not been studied. We can only speculate regarding the same. This can find its origin in the MoCA (e.g. depressed patients scores lower) or in the diagnostic route of cognitive impairment (e.g. taking depression into consideration). The lack of motivation, which is part of depression, will influence cognitive functioning.

If we look at the MCI-neurodegenerative group, the figure 2b of Chapter 4, shows a wide variation in total MoCA scores. Even though the patient has a low MoCA score, as it appears later, the clinician diagnosed these patients as not having dementia. Although we do not know the exact motivation of the clinician in these individual cases, we can speculate that one of the main criteria for dementia, some interference with independency in (I)ADL, were not being met. Again, clinical expertise seems to 'overrule' (or not be in line with) the MoCA score. This is also how it should be.

Needless to say, all these observations underline that a study result seems to give a fixed and rigid result for the study group, especially with validating a test, but in clinical reality, many demographic and clinical characteristics should be considered as they affect the patient.

The fact that many individual factors are actually considered in a clinical assessment can also be seen by the distribution of the two control groups in our study, that is, the screened versus the triaged controls. The MoCA range is smaller if the clinician's estimation of whether there is possible cognitive impairment is included in the inclusion criteria: 12–30

instead of 3–30. Specificity increased even though the control group became more like the disease group; namely, the three groups (i.e. MD – MCI – NoCI) were all suspected of having cognitive symptoms. Referred patients in whom there was an obvious other cause were apparently excluded from the group 'suspected of having cognitive symptoms' after the initial assessment even if there was a (very) abnormal MoCA (in retrospect). This indicates that the clinician does not worry about cognitive impairment, for example, as it was temporary, or sees other (reasons why these patients present) symptoms that could affect the MoCA score, such as lack of motivation. Conversely, the effects of having few selection criteria for a cohort and without correction (by clinicians) due to individual factors (of the patient) is highly objective but introduces outliers. Although taking account of individual circumstances may be the obvious thing to do in clinical practice, not being able to do this is has consequences for a cohort study, as designed in Chapter 3. The advantage of not excluding anyone, automatically entails that everyone also participates and resembles more of a 'blind' screening situation. However, this will include the obviously unmotivated or manic patients. With an 'open' screening, that is, taking the clinical situation into account, the test assessment would perhaps have been delayed or at least the score would be reviewed in that light. However, to avoid arbitrariness or the influence of the examiner and thus introduce unwanted subjectivity, inclusion and exclusion criteria are used to prevent subjectivity. Due to the study design, this will then create false negatives and false positives that would normally be filtered out in daily practice. Subjectivity and clinical perspective seem to be the same here but are respectively feared (in research) or desired (in clinical practice) depending on the reason for taking the test. Our study attempted to maintain objectivity with respect to included patients, despite the exclusion criteria. However, there is room for comment on this. For example, referred patients who were already known to have moderately severe dementia were excluded. In doing so, we made it more difficult for the test because, again, the groups to be distinguished became more similar: patients with obvious dementia were excluded and (most likely) with them, MoCA scores in the lower ranges. Even though this met the STARD-D criteria (Noel-Storr *et al.*, 2014), avoiding the extremes of the spectrum. Thus, healthy controls should also be considered an extreme of the spectrum.

All the above considerations can be summarised as follows: Do not just implement or rely fully on a cut-off score provided by a researcher. This is especially true for a positive MoCA. Judge a bedside test by its total score but always include your clinical knowledge (of clinical and demographic characteristics of the individual patient) and observations, including how the MoCA score was obtained. Use the strengths of the test and know its weaknesses.

7.3.2 Considerations of Section C: The MoCA in clinical practice

In this section, we highlight the practical possibilities of the MoCA. This is based on our findings, as described in Chapters 5 and 6. In the daily use of the MoCA, many clinical users always interpret it with a margin of uncertainty. This involves, if all goes well, the clinical history of the patient, as assessed by the examiner. In doing so, a great deal of subjectivity is influential. In a positive sense, this subjectivity is referred to as the clinical view. However, this 'subjective' clinical view can help make the right decisions when the interpretation of a dichotomous result is not as certain despite what the cut-off situation may make apparent. As argued earlier, subjectivity is desirable in practice, of course within limits, but not in scientific studies. We have translated the clinical and intuitive use of the MoCA, where a margin of uncertainty or error is often used, into a study design. The seemingly intuitive 'double cut-off point' introduced in clinical practice consists of a score where the examiner is not sure how to interpret the score, that is, a grey area. This automatically creates two states on either side of the grey area: one area where the examiner is certain of the negative result from the test (no cognitive impairment), and one area where the examiner is certain of the need for a neurocognitive evaluation based on a positive MoCA test. Our double-threshold study shows that a grey area does not only mean bad things. This can also bring about benefits. We examined the range within which this grey area should be located with a higher certainty of the outcome of the MoCA compared with a single cut-off point. Our results, combined with results presented in the existing literature, show that even patients with a false positive test (i.e. MCI below 21) are more prone to develop dementia sooner than patients with MCI who score above this cut-off. Therefore, even though these MCI patients are to be rated as false positives, one could consider these true positives for an elaborate neurocognitive assessment. This can be considered a correct referral for various reasons, with an early diagnosis being one of them.

These two chapters provide seemingly opposing advice. On the one hand, we show the risk of using the MoCA as a standalone or 'blind' screener (e.g., false positives) and confirm the added value of using the MoCA when used as an add-on, that is, triaging (Chapter 5). On the other hand, the case report in Chapter 6 demonstrates well how the MoCA can be of great clinical significance, even in the presence of a good result (during routine collection or screening). The add-on strategy, meaning using the MoCA after clinical judgment, clearly shows better results in terms of accuracy, PPV, and reduction of referrals compared to using the MoCA without any clinical judgment (standalone). This seems to advocate against screening and only for triaging, but it actually shows that the

MoCA should not be used without clinical judgment. It is clear that the reason for assessing the MoCA influences the outcome and interpretation of the outcome. Examiners need to be aware of this issue. There are motivations for using the MoCA in both situations. Clearly, the advantages of using the MoCA as a triaging instrument, meaning after clinical judgment, are proven: fewer (false positive) referrals. When used with a double cut-off, some of the disadvantages will even be solved (fewer misclassifications) and more advantages will even appear (intermediate state policy). This seems to lead to the conclusion that MoCA should be used on indication only, but it actually underlines that the clinical view should be in the lead. The MoCA should never be used 'blind', it is a tool, not a doctor. Given the nature of the population in old age psychiatry, there is a strong case for screening all referred patients for cognitive impairment. Maybe we should not consider it only screening but also getting their baseline as this population is not only at a higher risk of having cognitive impairment but also of developing it in the near future than the general population. The case report seems to be an isolated example, but in my experience, there have been many examples in which having a baseline MoCA was very important. As our studies have shown, screening can create many false positives, especially when applying the original cut-off score. However, using the double threshold substantially reduces the false positives on one side and gathers baseline scores on the other side, which can be very helpful. In addition, as explained earlier, the cohort design of the study introduces more false positives, as it is 'blind', by not being able to correct for low MoCA scores due to obvious non-cognitive aetiology. In clinical practice normally a correction of these false positives, for example a low MoCA score due to intoxication, would take place.

Again, when the MoCA is used as a screener, the examiner should not, and hopefully will not, only look at the MoCA score itself, but also take all elements into consideration. This will, together with the double cut-off, further enhance the MoCA's accuracy in clinical practice. The MoCA should not only be used on indication but also to get an indication.

Another example where study and clinical reality do not (or cannot) match is the scientific confirmation of a third cut-off point, meaning that below a very low MoCA score, no referral to a memory clinic is needed to confirm dementia. As mentioned in Chapter 5, this is not feasible on the MoCA score (alone), as the PPV is never high enough to be sure of a dementia diagnosis. However, PPV considers only the MoCA score in this study. In clinical practice, when there is a patient with a clear course (including advanced age) suggestive of dementia, and there are no other signs or symptoms suggestive of other (psychiatric) aetiology with a very low MoCA score, further follow-up investigations are often not initiated.

7.3.4 Implications for clinical practice and health policy, and recommendations for future scientific research

In the foregoing discussion, we recapitulated what we presented in this dissertation, but what are its implications for clinical practice, and what evidence is still missing? How could we close that gap in knowledge so that a better health policy can be formulated?

The clinical implications of the validation of the MoCA in old age psychiatry are, in our humble opinion, numerous. Different advocacy groups recommend making more diagnostic efforts. This was accompanied by public campaigns. More people seek reassurance for minor complaints, but subjective complaints do not always correspond with objective impairment, whether it is reported by a next of kin or by the patient himself (Pendlebury *et al.*, 2015; Ryu *et al.*, 2020). This dissertation shows that the MoCA is very useful for ruling out cognitive complaints. Even though one can argue that the use of the MoCA was already implemented in old age psychiatry, we added scientific proof that it does what we think, or hope it does. More importantly, we now better understand how to use it and how to interpret the total score in old age psychiatry. The advantages and disadvantages of using the MoCA, instead of the widely used MMSE, are presented in this dissertation and seem evident. However, even during this research, policymakers still argued for restarting the use of the MMSE instead of the MoCA. The MoCA is proven to be a useful screening test in old age psychiatry for unseen cognitive impairment, excluding cognitive impairment during subjective cognitive impairment that is often experienced in old age psychiatry by patients as it can rise due to age, psychiatric diseases, or psychotropic medication. In addition, the side effects of pharmacotherapy can be evaluated by the MoCA, as these complaints are a major reason for therapy discontinuation, whether they truly exist or only subjectively do so (Gitlin, Cochran and Jamison, 1989). The MMSE is not up for that task, as it not only has a low sensitivity for MCI it also has a low credibility according to the patients to disprove cognitive impairment (Kerwin, 2009). In addition to screening, it is of great significance to triage who is and who is not in need of a scarce NPA. This is of great importance as the number of referrals is large and will continue to rise in the near future. It is expensive, scarce, time-consuming, and burdensome for the patient to perform this procedure in specialised outpatient clinics by means of an extensive cognitive examination, and sometimes includes an MRI, EEG and spinal fluid puncture. Therefore, a validated bedside test before a referral is desirable. This should meet the requirements of a short acquisition time, test multiple cognitive domains, and have good sensitivity and specificity for MCI. The MoCA meets all these requirements. For general practitioners (in the Netherlands), the MoCA is advised to be part of the diagnostic algorithm (Janssen *et al.*,

2017) as it is also advised to be used by the Cochrane and Alzheimer International Society (Davis *et al.*, 2013; Alzheimer's Disease International, 2018).

In addition to this, there are other reasons for a good validating test:

-For the 'diagnosis' of MCI, the course is uncertain, 20% of recovered 40% remain stable, and 40% are diagnosed with dementia after 3.5 years. Therefore, it is important to monitor the patient population. The MoCA can be used for this task (Krishnan *et al.*, 2017).

-For current drug therapies for dementia, it is important to be able to properly distinguish between MCI and dementia, because in the former, any benefits of medication, such as cholinesterase inhibitors, do not outweigh the side effects (Nederlandse Vereniging voor Klinische Geriatrie, 2014) and can even be potentially harmful.

-The high expectations that treatments will eventually be found for some causes of dementia, where early diagnosis seems essential, also contribute to this.

Therefore, the MoCA can be used for screening, as an add-on test for triaging or obtaining a baseline function and the MoCA can be used for active follow-up of cognitive function. The latter is important in old age psychiatry, where the prevalence of subjective as well as objective cognitive impairment is high. This includes follow-up of cognitive impairments accompanying psychiatric diseases. In all these cases, the MoCA has advantages over the MMSE as it is more sensitive to MCI. In a study by Rodrigues-Ramirez only 8% compared to 69% of patients with schizophrenia scored below cut-off on the MMSE or the MoCA respectively (Ramírez *et al.*, 2014). Currently, the administration of the MMSE also requires a fee to be paid. The MoCA also has advantages over an elaborate neurocognitive assessment in the aforementioned situations because it is faster, easier to apply (less specialised staff needed), less stressful for the patient, less costly, and reduces the waiting list for NPA.

So the use of the MoCA in old age psychiatry settings is substantiated by arguments, but there are still different ways to use it. Therefore creating different prevalence and because of this different accuracy. This depends on the local circumstances, whether one only wants to use it on indication from the patient (objectifying or reassuring), an indication from the clinician (triaging), or as a screener or even as a baseline tool for all referred patients to old age psychiatry settings. As our study shows, one should be aware of the influence that psychiatric diseases can have on the MoCA score, among other clinical and demographic factors, and that this can have, but often does not have, a big impact on the total score. Although our study suggests that the MoCA cannot differentiate between patients with MCI due to neurodegenerative causes or MCI due to psychiatric causes using

the MoCA total score, more detailed studies are needed. Are certain cognitive domains more prone to impairment than others due to their underlying aetiology? In the literature, there is evidence that some MoCA items do not contribute (as much) to differentiating between different aetiologies or even states of cognitive impairment as other items do. Most surprisingly, orientation is among them. Therefore, there is a shorter MoCA under development, for example, Basic MoCA (Julayanont *et al.*, 2015), finding the optimal short Mini-MoCA [https://www.mocatest.org/reference/] as well as digital versions (Berg *et al.*, 2018) under investigation to save time but with the same high reliability.

In the literature, subtle differences are mentioned in cognitive impairment, when present, of depression, schizophrenia, and bipolar disorder. These are illuminated in the paragraph 'definitions' of Chapter 1. In short, unipolar depression seems to affect cognition less than bipolar depression. The bipolar profile resembles that of a schizophrenic patient, although less severe (Van Rheenen *et al.*, 2017). However, is the MoCA sensitive enough to detect these differences? Alternatively, can it detect differences in neurodegenerative aetiologies, as there are differences found (at group level) in domains (Freitas, Simões and Santana, 2014; Coleman *et al.*, 2016)? Figure 2b in Chapter 4 shows that the total score (particularly on an individual basis) cannot be differentiated. However, can different domains or items be helpful? Future studies should attempt to answer this question.

In addition to differences between diseases, there is increasing interest in and evidence in the literature regarding the heterogeneity of cognitive impairment in certain psychiatric diseases. It is even suggested that differentiation by nosological aetiology, such as bipolar disorder, can or should be distinguished by different entities based on their cognitive profile (Van Rheenen *et al.*, 2020). Bipolar patients with more cognitive impairment, resembling schizophrenic cognitive profiles, will have more psychotic features than bipolar patients with less cognitive impairment. This could explain why no specific cognitive profile is found for these psychiatric diseases, as they are categorised by diagnostic categories and less by functional or dimensional features (Van Rheenen *et al.*, 2020). This problem also accounts for the use of the MoCA. However, as our results show (figure 2b), the MoCA could differentiate between the three suggested groups of no, mild to moderate, and severe cognitive impairment in bipolar patients. The MoCA could therefore be of added value for the 'large, longitudinally focused studies of cognition' that are required to better 'define cognitive trajectories' in psychiatry and bipolar disorder specifically (Van Rheenen *et al.*, 2020) as it is easy and inexpensive to implement, but mostly as it is more sensitive for mild cognitive impairment than the still widely used MMSE in (general population-based) large longitudinal studies.

Another query where the MoCA could be of help is whether cognitive impairment worsens after every episode. There is literature indicating that in unipolar depression, the cognitive deficits worsen with repeated episodes (Ahern and Semkovska, 2017; Riddle *et al.*, 2017; Semkovska *et al.*, 2019). There is evidence of a correlation between the severity of episodes and the amount of global cognitive impairment (McDermott and Ebmeier, 2009). However, in bipolar depression, studies show comparable deficits after the first episode or recurrent episodes, including late-life bipolar disease patients (Bortolato *et al.*, 2015; Szmulewicz, Valerio and Martino, 2020). Other studies note that older patients seem to have more cognitive deficits than their younger counterparts (Hashem *et al.*, 2017; Dols and Beekman, 2020; Mukku *et al.*, 2021) but this can be independent of repeated episodes. Problems in concentration and attention, which are part of the diagnostic criteria of affective disorders, can influence different domains and therefore be the reason for not finding a specific profile but a more global impairment. Although information processing (processing speed), memory, and executive deficits can be prominent, apraxia, aphasia, and agnosia are rare. Lack of motivation, which is part of depression as well as of a manic episode, influences cognitive functioning. Executive dysfunction that causes impulse disinhibition is one of the diagnostic features of a manic episode.

As for patients with schizophrenia, considerable data shows that cognitive impairment remains stable after onset (up to 10 years of follow-up) (Rund *et al.*, 2016) indicating that overall cognitive impairment seems independent of the (duration of) psychotic episodes (Bortolato *et al.*, 2015). The above-mentioned relationship between cognitive severity and number of episodes is still debated to some extent, and large longitudinal studies could further help to solve this issue. However, this should include the heterogeneity of cognitive impairment associated with these diseases. Therefore, another opportunity for the use of MoCA is to differentiate cognitive heterogeneity in these follow-up studies. A question that remains open is whether the total MoCA score or some impaired items develop or recover differently with different aetiologies. One hypothesis is that if the MoCA is impaired due to depression, this could recover to a certain amount, whereas the MoCA (if indeed impaired – as this differs greatly between individuals) of patients with schizophrenia would not recover (as much). The latter is also found in a study by Wu where the overall cognitive impairment did not recover on the MoCA during acute hospital stay and across symptoms changes with schizophrenia (Wu, Dagg and Molgat, 2017). However, the MoCA scores of patients with MCI due to neurodegenerative causes are expected to deteriorate over time. A longitudinal study can answer these important questions. A longitudinal study could also shed light on the often-used method of repeating the MoCA after the psychiatric symptoms have

subsided. This method is often used in clinical practice, although it has not been proven whether it is the correct means to distinguish between a low MoCA score due to psychiatric causes and a low MoCA due to neurodegenerative causes.

Another subject that must be studied further is combining the MoCA with other 'bedside' assessments measuring other aspects of the diseases to improve accuracy, but not the cost in time or budget. In addition, bedside tests often require less-trained staff. This is, next to budget, a major issue in the near future, as fewer specialised staff are expected in proportion to the number of patients due to demographic changes.

The clinical implications of the study on valproic acid were not only to learn from our mistakes but also to warn others. Furthermore, it also changed the protocol of the request for concertation for valproic acid at our hospital and in the region. Ever since our publication, albumin blood levels are always measured when the total concentration of valproic acid is monitored. In addition, it has become easier to request a free blood concentration in the laboratory these days with less argumentation. Of course, it would be better to add the free valproic acid level from the beginning, as it is the standard in some countries, such as Japan. This decision is for health policymakers to make, as it comes with some extra cost. However, the implemented new policy of adding albumin blood levels will not avoid all unseen and avoidable side effects of elevated free valproic acid levels. We still recommend measuring free valproic acid levels, especially in the older adult population. The albumin level itself is also relative. The literature mentions a lower binding capacity of albumin in older adults, next to the effect of other medications that have a higher affinity for binding to albumin, such as NSAIDs. This increases the free fraction of valproic acid and the risk of side effects. Even if the clinician is aware of the side effects of valproic acid, the following case is easy to imagine: a patient of age who used valproic acid for years recently starts to complain about cognitive impairment. He asks his doctor, if at all this could be due to the use of valproic acid. If the total valproic acid blood concentration stayed the same an understandable reaction of the doctor would be 'if the side effects did not start at the start of the treatment; there is a very low likelihood that it will emerge only after years'. Even so, if the doctor is willing to check the valproic acid level (as it should be routinely) to exclude a rise, she will get the total blood level. This can be the same for all the previous concentrations. Even with a normal albumin value accompanying the therapeutic total valproic acid concentration, the free valproic acid concentration can still be elevated owing to lower binding capacity because of age or other medications. The reason for the cognitive impairment remains unnoticed and is likely attributed to age or (if they have read this

dissertation) to the underlying disease for which valproic acid is used. Unfortunately, we do not know how often this imaginary example occurs in clinical practice. We (still) do not know the prevalence of patients with therapeutic concentrations of total valproic acid and elevated concentrations of free valproic acid. A study by Wallenburg mentioned that 37% of the requested laboratory measurements of free valproic acid concentrations, because the patients were at risk of having low albumin concentrations, showed unbound concentration above threshold (Wallenburg *et al.*, 2017). Only 12% of them had elevated total valproic acid concentrations. Future research should investigate the percentage of all patients, especially in an older population, that use valproic acid and have 'normal' total blood concentrations but have elevated free valproic acid concentrations. By knowing these numbers, not only can the costs and benefits of reporting the free fraction be weighed against each other, but one can also be more aware of its prevalence. If this missing information is at hand, taking the Wilson and Jungner criteria into account, screening for the elevated free concentration of valproic acid could be advised, as monitoring the total concentration is already part of international guidelines when valproic acid is used. This is important for avoiding intoxication in the future. However, equally or even more importantly is when the side effects of valproic acid stay subtle, such as cognitive impairment, and can easily be wrongly attributed to other causes, such as ageing. In particular, as more patients will suffer from these fewer extreme side effects, in contrast to our case study, these will still have a high impact on the health and quality of life of valproic acid users. Again, we cannot underscore often enough that this case report is a perfect example of why baseline MoCA scores should be considered in old age psychiatry as a standard procedure.

As we have seen in the study of Needs in Bipolar Older Adults, for recovery, the 'No or Met Needs' are important not only in the 'physical domain' but also on the 'social' (or societal) level. The needs in this (these) later domain(s) can negatively affect quality of life, the number of needs, and doctor visits (Chapter 2). Recovery can occur in multiple areas: clinical, social, functional, and personal. Due to the patient's perception that he or she still has care issues or unmet needs and has not fully recovered in one of these areas, he or she will continue to experience symptoms and ask for care. Even though in the clinical area, the patient has (largely) recovered in the eyes of the practitioner, this could (possibly) not be so in the eyes of the patient. If this is not recognised by the practitioner because it remains invisible or unknown to the practitioner, it will lead to misdiagnosis or, to put it mildly, to the treatment of only the clinical diagnosis and not of the bigger problem. Not being able to initiate a suitable 'total' treatment that can lead to a satisfactory recovery in other areas of this bigger problem can generate unnecessary extra costs. This

is partly due to the reciprocal nature of the demand for care for the psychiatric complaint (Houtjes *et al.*, 2011). There is also considerable evidence in the literature regarding the need for functional, social, and personal recovery. In doing so, 'there is no hierarchy or imperative order' (stel van der, 2015) between the different aspects of recovery. Even if it is not one's competency or primary mandate to address the 'other' or 'all' areas of recovery, the clinician must be aware of them and therefore can refer the patient to a facility or staff member where there is such a possibility, for example, social psychiatry. The treatment or treatment setting can then better match the treatment demand. For example, treatments with a clinical focus that is inappropriate for social or functional recovery due to an underlying social need can be reduced. This results in reductions in the number needed to treat by reducing the number of aforementioned misdiagnosed patients and the associated number of unnecessary treatments (Stel van der, 2015), thus reducing the cost impact. In addition, the number of unmet needs can be reduced, and the quality of life improved. We want to highlight the apparent watershed between the reported needs being met or not on the basis of the CANE between patients and staff. This seems to be the same partition as a realistic or daily practice versus theoretical or idealistic psychiatric treatment. As one can debate whether all CANE items belong to the primary goal of psychiatric care (clinical recovery), one cannot debate whether these unmet CANE items will influence the wellbeing of patients and play a part in functional and social recovery. This is a clear message not only for clinicians, but also for policymakers and insurance companies, and they should be aware of this.

There is also an increasing tendency to assess the needs of patients (Thornicroft and Slade, 2014). The CANE has been used to assess the needs of older psychiatric patients and those in general practice.

In the UK, both the Department of Health and the Royal College of Psychiatrists recommend CAN(E) as an 'outcome measure' to be used by mental health professionals who wish to make sure their clinical practice is effective (http://www.kcl.ac.uk/ioppn/about/difference/The-Camberwell-Assessment-of-Need.aspx). In the Netherlands, it is one of the core instruments that comprise CNCM, the cumulative needs for care monitoring, used to plan treatment for individuals, and conduct research (Drukker *et al.*, 2007). The CAN(E) is often used as an aid during the history of complaints interviews, which follows the demand-oriented care in the mental health sector (HOI or herstelondersteunende intake).

As the CANE is used in multiple studies using different inclusion criteria, we raise the question of what could be learned from these results.

Do different patient or population characteristics give rise to different needs and to different amounts of meeting these needs? Is there a difference in the ratings of patients and their (professional) caretakers? First, the benefits of this gathered information can be helpful for the primary healthcare process, as well as for policymakers. On an individual level, it shows where the needs are, so the treatment can be customized for the individual patients' recovery, not only in the clinical domain but also in the functional and social domains. Second, for specific patient groups, it highlights where the treatments are effective in countering the needs and where the lacunae are so that policy can be adjusted. There is even greater urgency to understand the needs of older patients due to ageing, especially because there is uncertainty if there is an increase in met needs, as age seems not to be correlated to unmet needs, and if this is due to a shift in needs or merely a rise in the same needs (Lloyd, King and Moore, 2010; Meesters *et al.*, 2013). Finally, a comparison between different diagnostic groups can highlight if there are differences in needs, especially unmet needs. Not only can we try to determine why these differences exist, but a more effective policy can also be adopted.

Based on our results and the available literature, we hypothesise the following: 1. Overall, older (psychiatric) patients have the same items of needs and unmet needs as their younger counterparts. Except for diagnose specific items such as memory for dementia and patients' demographic characteristic-specific needs such as incontinence for age. 2. It is the amount of these needs that differs between populations and is influenced by the degree of disability or recovery. 3. We speculate that if their disability is more comprehensible, these needs will be better met, and the discrepancy between the rating of the patients and their caregivers will be less. However, we hypothesise that this will be the case for items that belong to the core treatment of medical psychiatry (i.e. clinical recovery), and less the case for items that can be attributed to functional as well as social recovery.

Future studies should examine whether these hypotheses are correct. A major contribution would be to study the needs of middle-aged patients with bipolar disorder so that these can be better compared with our results. Assessments with CANE/CANSAS or CAN can provide valuable information at these three decision levels. This is done by knowing and comparing the needs and unmet needs of the individual patient, within a group (intragroup), and between different groups (intergroup).

7.3.5 Applying the criteria of Wilson and Jungner (1968) to the MoCA as a screener for cognitive impairment.

As mentioned in the introduction, the interpretation of the three concepts *Need, Demand,* and *Supply* (Need: What people benefit from; Demand: What people ask for; Supply: What is, or could be, provided), viewed from the perspective of Bradshaw's taxonomy, are prone to change over time as knowledge and resources will change even though their meaning will remain the same. These three concepts will have a major impact whether to screen or not. We hope that the results presented in this dissertation with these three concepts of Bradshaw in mind, will add to address the Wilson and Jungner criteria. However, our answers are by no means complete and are prone to change with time as knowledge (of the expert, the patient or the community by new research) and resources (budget as well as new tests or techniques) will keep changing and will influence the answers to the four questions asked by Bradshaw. What does the expert know, what does the patient feel, what does the patient express, and what do other patients do (Bradshaw, 1972)?

We focus in this paragraph on the MoCA as a screener however the Wilson and Jungner criteria could or even should be applied to the other 'screening instruments' we used in this dissertation, i.e., the CANE and valproic acid concentration. Especially the 'free valproic acid concentration screening' as it is not implemented in guidelines of most countries when patients use valproic acid, in contrary to screening the 'total valproic acid concentration'. This is exemplary of the shift of knowledge that could influence the outcome of the Wilson and Jungner criteria on whether guidelines should recommend to screen with free instead of total valproic acid concentration. As a lot of the Wilson and Jungner criteria on this topic cannot (jet) be answered sufficiently we cannot come to conclusion by these criteria. Most notably criteria 1, 3, 7, and 9 as they refer to the prevalence, adequate facilities for detecting, the course and the cost which are not jet clear in the case of an elevated free concentration during therapeutic total valproic acid concentrations.

1 The disease to be detected must be a major health problem.

First, we want to note that cognitive impairment is not a disease but a state, as explained in Chapter 1 and 5. This does not mean that cognitive impairment cannot be a major health problem. Even if we look at mild cognitive impairment. The qualifier 'mild' only refers to something about the degree of symptoms or the state of the condition. However, the consequences can be significant. Although the definition of MCI states that the impact on IADL and ADL should be minor, the emotional consequences of awareness of change do not have to be. Another way of looking at these criteria is to consider this not only

for individual patients but also for the overall health system. Dementia and cognitive impairment are leading causes of dependency and disability, respectively. It currently affects approximately 10 million people in Europe, and its prevalence is expected to double by 2030. Dementia occupies (in 2019) the seventh place among causes of death and disability globally (*WHO mortality-and-global-health-estimates*).

2 There must be a generally accepted method of treatment for the disease.

If we consider the treatment of cognitive impairment from a wider perspective, there are multiple levels where one could expect the effect of a treatment. Treatment is not only to treat the disease, but also the condition that comes with it. The treatment should not only be focused on the patient but also on its environment, including their informal caregiver. Special attention should be paid to dealing with patient needs, including behavioural psychological symptoms of dementia (BPSD). In addition, the guidance and monitoring of needs at home are part of the treatment. The MoCA can be part of this monitoring.

Another view on treatment could be to obtain the correct (diagnostic) route. Here, the MoCA can be of added value in this process, as explained in this dissertation. It is not only now validated for old age psychiatry, but we showed it can add substantially to improve referrals.

Furthermore, the WHO, among other advocacy groups, states that early diagnosis of dementia is necessary (*WHO Global Action Plan on the Public Health Response to Dementia 2017–2025*; Prince, Bryce and Ferri, 2011). It is hoped that early diagnosis can be of use in either finding a cure or using this treatment in the near future. As for now, early diagnoses can help prepare patients for things to come. He or she can still be in control of decision making, which is inevitable. As shown in this dissertation the MoCA could have a role in this process.

3 There must be adequate facilities for diagnosis and treatment.

This is a major concern at present but will be even more so in the near future because already, 50–90% of cases of dementia remain undiagnosed in high- to low-income countries, respectively, and there are already shortages of 'adequate facilities' (Alzheimer's disease International, 2016). The MoCA, as shown in this dissertation in Chapters 3, 4, and 5, can contribute significantly to this through not only screening and early detection, but also by reducing false-positive referrals by triaging, thereby relieving the diagnostic pathways. As for the MoCA itself, the studies presented in this dissertation contribute to the criteria for adequate facilities, as the MoCA is now validated for these facilities.

4 There must be a recognizable latent or early symptomatic stage of the disease.

As mentioned in Chapter 5, cognitive impairment is a continuum where the 'disease', as in dementia, or 'health' is identified by using classifications. These classifications are on either side of this continuum, creating states that are neither dementia nor 'without cognitive complaints'. As mentioned in Chapter 1, the criteria for this intermediate state (MCI) are constantly evolving, with a tendency to capture more precise precursors of dementia without including the state of mild impairment due to other aetiologies such as several psychiatric disorders. A frequent mistake is that one considers MCI as a state before dementia in a categorical way, as it were. This mistake is understandable, as MCI increases the probability of converting to dementia substantially. This is even true when the cause is a depression for example. So if we look at MCI as a *probability state* it is most certainty 'a recognizable early symptomatic stage' of 'being at risk' to progress on severity and rating scales of cognitive impairment like the CDR and GDS in the near future. Still, experts should become more aware that MCI is not exclusively an early stage of dementia and we hope this theses adds to that. The diagnosis of MCI, when using a screener, is often only based on the (quantitative) cognitive impairment alone, translating to 'less than dementia'. This phrase almost automatically implies MCI is an 'early stage of dementia'. Of course a problem is that subjective complaints and informer reports often do not correspond to objective impairment. So without an objective test, it is difficult to recognise MCI, regardless of whether it should be considered a latent stage of dementia. However objective impairment, which is in my opinion not the same as a positive cognitive test, should also incorporate the qualitative component as well, the demographic and clinical characteristics of the patient so to speak. The MoCA fits the task to be this objective test, as it is shown to be reliable, fast, and easy to use. However the MoCA measures only the quantitative part, and it does not incorporate the qualitative part which can add to the differentiation between aetiologies, as an NPA normally would do. The MoCA cannot, as shown in Chapter 4, recognize the latent stage of dementia (MCI-ND) among all MCI's, as to many cognitive impairment of other aetiologies meet the (quantitative) MCI criteria too. As shown in Chapter 5, using a double threshold, the MoCA can add more differentiation, as MCI patients with a lower MoCA (<21) have a higher probability of conversion to dementia than MCI patients with a higher MoCA score (≥21 MoCA <26). Therefore, if we consider 'the disease' as it is used in the criterion 4, being at high risk of (having or getting) severe cognitive impairment, the MoCA can identify MCI, meaning being at risk of conversion, and fulfil the criteria number 4.

5 A reliable detection method must exist.

What is considered reliable? Is it the same as the gold standard? Is the gold standard reliable (Coart *et al.*, 2015)? In this dissertation, the gold standard is considered to be the elaborate diagnostic route required by international criteria, even though they even come with uncertainties. This is well illustrated by the additions 'possible' and 'probable' (McKhann *et al.*, 2011) by the NIA-AA/NINCDS-ADRDA or, as stated in the DSM-5, where the criteria minor and major NCD include the amount deviations in standard deviations from the healthy mean. In this dissertation, we investigated the reliability of the MoCA, as this was not yet clear for an old age psychiatry setting. Taking the above into account, we still make the bold claim that a reliable diagnosis of 'no cognitive problems' can be made with the MoCA (≥ 26). Using a double cut-off we can add 'possible in need of an elaborate cognitive assessment (≥ 21 MoCA <26)' and 'probable in need of an elaborate cognitive assessment (<21)'. By keeping these phrases in mind, one could consider a very low MoCA score accruing with other clinical data fitting dementia, and other causes have been ruled out as an indication for possible dementia.

6 The detection method must be acceptable to the public.

In clinical practice, not everyone with complaints wants to know the reason for these complaints. In particular, regarding cognitive impairment, some are afraid of the results or consequences. Some prefer to ignore or downplay their complaints or attribute them to normal ageing. Some just don't think it is worth the effort (of getting an Neuropsychological assessment). However, this puts the clinician in a dilemma, as we know that unseen needs can lead to lower quality of life, more healthcare consumption, and lower overall health. Especially for cognitive functioning, it is often necessary to know the patients' impairment so that the treatment can be adjusted accordingly. This is not only important for psychotherapy, or avoiding dangerous foreseeable situations, but also for pharmacotherapy, e.g., ranging from finding cognitive side effects towards to what extent patients can use their medication safely without assistance. Using the MoCA can be of help to indicate whether the clinician should consider the cognitive capacities of the patients while prescribing. In addition, the MoCA has a low burden on the patient in terms of time and cost compared to an elaborate neurocognitive assessment. The MoCA can also add to follow without too much burden on the course of cognition, especially when compared with an elaborate cognitive assessment.

7 The natural course of the disease to be detected must be known.

As explained earlier cognitive impairment should be viewed as a state, not a disease. The underlying aetiology is the disease; therefore (often) the natural course of cognitive functioning is known when this aetiology is known. This applies particularly when a state of dementia is attained. For the cognitive state of MCI, this is less true, as the aetiology is often less clear. It is not a prodromal state of dementia but a probability state of converting to dementia and can have different aetiologies that can have different courses compared to dementia. It is known that a substantial proportion of patients with MCI will not convert to dementia, and for some patients, even the cognitive complaints diminish. Patients with MCI generally have a higher probability of developing dementia in the near future compared to people without an MCI in their history. Even if the patients seem to have recovered clinically, functional recovery may not be complete. This could be partly due to residual cognitive symptoms. Does the above imply that Wilson and Jungner's criterion is not fulfilled for cognitive impairment? We don't think so. Strictly speaking, if the aetiology is known, the global natural cause of the disease is also known. The MoCA can even be of added value in understanding the course of cognitive impairment to see whether it progresses, stabilises, or even diminishes. Therefore, by using the MoCA one can predict future courses better for patients with cognitive impairment.

8 There must be agreement as to who should be treated.

As with criterion 2, we have to clarify what treatment should be considered. Adding to the arguments mentioned in criterion 2, we want to include, from the perspective of the MoCA, referral to a memory clinic as treatment. From this perspective, we add supporting motivation to this criterion 8 of Wilson and Jungner through our study presented in Chapter 5. Although one can (still) debate what kind of 'treatment' the different suspected and triaged patients should receive, we substantiate arguments on how to use the MoCA for who is and is not to be referred to a memory clinic ('treatment') and who is to be monitored actively.

9 The cost of detection, diagnosis, and treatment must be in an acceptable proportion to the cost of health care as a whole.

In Chapter 5, we demonstrate the benefits of using the MoCA as a screener. This brings not only advantages in cost as expressed by money, saving €1000 per avoided false positive, but also for the patients (e.g. less burden in time and stress) as well as for the clinic (e.g. using the facilities more efficiently, shorter waiting list).

10 The process of detection must be a continuous process and not a one-time project.

This criterion is, of course, part of a bigger debate and is also mentioned in this dissertation. This criterion combined with criterion 9, 'the cost must be in proportion', is of importance that the cost must not outweigh the benefits. This is especially true if one considers the use of a test not only for indication, that is, triaging, but continuously (i.e. as a screener). As often when there is a debate, the disagreement is often about the grey area between the two opposite views and where to draw the line: 'screening versus on indication only', 'general population versus high-risk population'. However, as is so often the case, 'who or how to screen' must first be a part of the topic for the problem to be solved. Thinking of screening for cognitive impairment and considering the above, the criteria 'the how' and 'the who' make a difference, that is, respectively, what test is used and the prevalence of cognitive impairment. Even though advocacy groups encourage more screening as they want to lower the number of missed cases of dementias, there is critical literature with different motivations related to this wish. Spending resources wisely being one of them. To solve these dilemmas, it helps to start at the extreme ends at either side of the grey area, where there is less doubt about the necessity to assess cognitive function. When starting this dilemma from one side of the population. i.e., prevalence, all the high-risk populations should indeed be assessed. Moving down in risk or prevalence, the relevance of criterion 9 will increase. This is where not only 'the who' but also 'the how' becomes important as the cost and yield differ per test. In general, with cognitive assessments, the more concise the test is, often implying to be cheaper, the less accurate it will be. To meet criterion 10, including criterion 9, one must consider how the inevitable interaction between 'who' and 'how' is tested. This interaction takes place between the continuum of 'the who': 'high-risk population (e.g., with subjective complaints) through the old age psychiatry patients to the general elderly population' and continuum of the how: 'extended testing with an elaborated assessment, through the MoCA towards the MMSE'. In this dissertation, we show the advantages of the MoCA that will help bring these contrasting black or white views, to screen or not to screen, closer together and even merge, by adding more colours (i.e. a double cut-off) to the grey area. As motivated in this dissertation, we showed that the MoCA is a valuable tool for the continuous screening of a population at an increased risk for cognitive disorders.

7.4 Concluding remarks

To screen or not to screen – that was the question.

Next to taking the Wilson and Jungner criteria into account, we are convinced that, in this dissertation, we have provided the arguments that the MoCA can play a substantial role colouring the grey area that this question raises. Therefore allowing (part of) this discussion to be settled for cognitive impairment. As subjective cognitive complaints do not always correspond with objective impairment, a fast and reliable bedside test is needed. This accounts especially in old age psychiatry where MCI is a frequent issue due to multiple aetiologies. What you see is not always what you get. This is also true for needs, unmet needs, and the free concentration of valproic acid. Unfortunately, the question to screen or not to screen cannot (yet) be answered on these matters. The MoCA is suitable for MCI screening in old age psychiatry, with its population at risk. However knowing its strengths and weaknesses is essential. It is better suited for detecting MCI than the MMSE, with fewer false negatives. The MMSE, with low false positives for dementia, can be used on one side of the uncertainty spectrum. An elaborated neuropsychological assessment is needed on the other side of the uncertainty spectrum to differentiate between different aetiologies of cognitive impairment. Between these two extremes the MoCA fills the gap perfectly for screening and triaging patients with an increased risk of developing or having cognitive impairment, including MCI; for example, in an old age psychiatry setting. It is faster, cheaper, and therefore easier to apply than a neuropsychological assessment; however, it will have difficulties in differentiating the aetiologies.

Therefore the MoCA should not only be used on indication (triaging) but also to get an indication (screening) in old age psychiatry.

If your MMSE score is wrong, then something is really going on.
If your MoCA score is right, then you should be alright.
If your MoCA score is so so, active monitoring is the way to go.
If your MoCA score is low, an elaborate assessment should follow.

We hope we have convinced the reader (for now) of the importance of knowing the strengths and weaknesses of a screening instrument in old age psychiatry.

Trust me, I am a validated test.....?

Trust me I 'm a doctor, and know how to use a validated test!

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CHAPTER

Appendix

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8.1 Nederlandse samenvatting

Inleiding

In de Ouderenpsychiatrie komen veel psychiatrische ziektebeelden samen. Simpel gezegd stoornissen in gedrag, gevoel, gedachtes en geheugen. Diagnosticeren en zorgbehoeften in kaart brengen is dan ook in de Ouderenpsychiatrie geen sinecure: hoe krijg je de dikwijls ongeziene of ongenoemde problemen boven tafel? Velen van ons denken dat de klassieke psychiatrische beelden zich zuiver presenteren: dementie komt met cognitieve stoornissen; depressie met stemmingsstoornissen en schizofrenie met psychotische stoornissen. Maar het wordt steeds duidelijker dat er een grote overlap is in klachtenpresentatie op oudere leeftijd. Dit komt niet alleen doordat de kans dat twee van deze ziektes tegelijk voorkomen toeneemt met het ouder worden, maar ook doordat de ziektepresentatie zich niet beperkt tot het klassiek geachte ziektebeeld, zeker op hogere leeftijd. Bij veel psychiatrische beelden treden comorbide cognitieve stoornissen op. Soms treden deze stoornissen zelfs eerder op de voorgrond dan het klassieke ziektebeeld zoals bij schizofrenie, waar de cognitieve stoornissen dan eerder merkbaar zijn dan de psychotische. Andersom worden vaak depressieve of psychotische klachten opgemerkt, nog voordat een dementie wordt vastgesteld, zoals hallucinaties bij een Lewy body dementie of depressieve klachten bij vasculaire dementie.

Een diagnostische uitdaging van andere aard, is dat oudere patiënten om diverse redenen niet altijd duidelijk verwoorden wat zij aan klachten beleven. Klachten worden niet altijd benoemd, zowel door de patiënt niet, als door de directe omgeving niet. Maar andersom komt ook voor: er worden subjectieve klachten ervaren die voor de dokter niet goed te begrijpen of objectiveren zijn. Dit is zeker het geval bij (subtiele) cognitieve klachten, zoals geheugenproblemen. In het ergste geval leidt deze mismatch tussen beleefde en vastgestelde klachten tot een zogenaamde ‘patients delay’ en ‘doctors delay’: diagnoses worden enige tijd gemist. Voor dementie is bekend dat 50% tot 90% van de diagnoses niet wordt gesteld, in respectievelijk ontwikkelde en arme landen.

Een uitgebreid neuropsychologisch onderzoek, onderdeel van de internationale gouden standaard om cognitieve klachten te onderzoeken, is een beproefd middel om subtiele cognitieve klachten te objectiveren. Er is een tendens gaande om steeds vroeger in het ziekteproces en met minder klachten te onderzoeken of de subjectief beleefde klachten bij een neurodegeneratief proces horen. Neuropsychologisch onderzoek is echter kostbaar en gekwalificeerd personeel schaars, terwijl het aantal oudere patiënten door demografische verschuivingen fors toeneemt. Een objectieve screener die makkelijk, snel en betrouwbaar subjectieve klachten kan objectiveren, is daarom van belang. Met zo’n test zal beter kunnen

worden bepaald welke patiënt uitgebreid neuropsychologisch vervolgonderzoek nodig heeft ('triageren'). In de ouderenpsychiatrie gaat het dan om een test die gevoelig genoeg is voor subtiele of milde cognitieve klachten (MCI). De in 2005 ontwikkelde Montreal cognitive assessment (MoCA), is gevoelig om MCI op te sporen. Deze screener zou een rol kunnen spelen in het bevestigen, of vinden van onopgemerkte, cognitieve stoornissen. De test is al gevalideerd voor verschillende settings, maar nog niet voor de ouderenpsychiatrie.

'Patients delay' en 'doctors delay' komen niet alleen voor bij het in kaart brengen van cognitieve stoornissen, maar ook bij gezondheidsbehoeften in het algemeen ('needs') van de patiënt. Hierdoor kunnen ook gezondheidsbehoeften van de patiënt ongezien en daarmee ook onbeantwoord blijven ('unmet needs'). Dit kan niet alleen leiden tot ontevredenheid bij de patiënt en verminderde therapietrouw, maar ook tot een verlaagde kwaliteit van leven en het niet kunnen aanpassen van de behandeling op de omstandigheden van de patiënt. De CANE (Camberwell assessment of Need for the Elderly) is ontworpen om de zorgvragen van oudere mensen met psychische problemen in kaart te brengen. Dit doet deze vragenlijst niet alleen vanuit het perspectief van de patiënt, maar ook vanuit zijn/haar naaste én de behandelaar.

Resultaten en overwegingen

Sectie A ongeziene zorgbehoefte.

De studie van dit onderdeel worden in detail in **hoofdstuk 2** gepresenteerd. Samengevat laat ons onderzoek zien dat de patiënten en hun behandelaar het grotendeels met elkaar eens zijn over de zorgbehoeften ('needs') die er zijn. Aan deze behoeften wordt ook grotendeels tegemoet gekomen door de behandelaar ('met needs'). Niettemin was een belangrijke bevinding dat behandelaren de zorgbehoeften in het *sociale domein*, zoals gezelschap en adequate dagbesteding, neigen te onderschatten. Deze schijnbare blinde vlek kan een kettingreactie van gevolgen met zich meebrengen, die de kwaliteit van leven van de patiënt aantast en zelfs voor een toename van (secundaire) klachten kan zorgen. De bevindingen onderstrepen de noodzaak voor behandelaren om verder te kijken; behandeling zou meer moeten behelzen dan klinisch herstel alleen. Sociaal, functioneel en persoonlijk herstel speelt namelijk een belangrijke rol in de algehele gezondheid en het welzijn van patiënten. Deze resultaten komen overeen met eerder onderzoek dat gedaan is naar de CANE.

Sectie B validatie van de MoCA in verschillende Ouderenpsychiatrie omstandigheden

Om een test goed te kunnen interpreteren moet deze gevalideerd worden. Het liefst in de te gebruiken setting. Daarom werden twee cohorten van patiënten onderzocht: 1. Een

cohort bestaande uit alle verwezen patiënten naar de Ouderenpsychiatrie (**hoofdstuk 3**) en 2. een cohort van patiënten die verdacht werden van cognitieve stoornissen in de Ouderenpsychiatrie (**hoofdstuk 4**). Voor beide studies gold dat de gemiddelde totale MoCA-score significant verschilde tussen alle drie de groepen, te weten milde dementie versus MCI versus controle patiënten bestaande uit respectievelijk verwezen of verdachte patiënten. De optimale afkappunten waren voor beide studies als volgt: dementie <21 en MCI <26. Om klinisch onderscheid te kunnen maken voor de *individuele patiënt* schiet de MoCA echter te kort, omdat de spreiding te groot is. Het is bekend dat sommige psychiatrische beelden (forse) cognitieve klachten *kunnen* geven, maar dat dit niet bij iedereen hoeft te gebeuren. Verschillende onderliggende oorzaken van MCI (MCI op basis van neurodegeneratief proces of psychiatrie) blijken niet van elkaar te onderscheiden door de totaalscore van de MoCA. Voor de klinische praktijk betekent dit dat een MoCA onder de afkapwaarde *ook goed bij patiënten kan passen met een psychiatrische stoornis.* In hoofdstuk 4 worden verdere handvatten gegeven voor de klinische praktijk.

Sectie C de MoCA in de praktijk bij de Ouderenpsychiatrie

Een voorgesteld afkappunt brengt naast voordelen ook onzekerheden met zich mee: gemiste diagnoses (zogenaamde fout-negatieven) en onterecht gestelde diagnoses (zogenaamde fout- positieven). Vandaar dat veel clinici in het dagelijks gebruik van de MoCA een onzekerheidsmarge gebruiken. Er ontstaat zogezegd een grijs gebied rondom het geadviseerde afkappunt. In **hoofdstuk 5** hebben we dit intuïtieve gebruik van de MoCA vertaald naar een studie met het gebruik van één, dan wel twee afkappunten. Daarnaast hebben we de verschillende selectiemogelijkheden voor een neuropsychologisch onderzoek (NPO) met elkaar vergeleken; op basis van alleen een klinische blik (na intake), op basis van enkel een MoCA score (stand-alone) of beide gecombineerd (add-on). De MoCA met twee afkappunten (<21 en ≥26) bleek het meest efficiënt en accuraat voor een NPO verwijzing. Bij een score onder de 21 bleek vervolgonderzoek zeer wenselijk, bij een score ≥26 bleek geen vervolg onderzoek nodig en met een MoCA score hiertussen in, kon een beleid van actief vervolgen worden geadviseerd, middels diezelfde MoCA Het gebruik van de MoCA als 'add-on' met twee afkappunten, gaf een reductie van 65% fout positieven verwijzingen voor een NPO ten opzichte van alleen de klinische blik. Deze klinische implicatie is, naar onze mening, zeer groot. Niet alleen vanwege de kosten, maar ook vanwege onnodige belasting van de afname van een NPO voor zowel de patiënt als de door wachtlijsten sterk onder druk staande zorg.

Het grotere thema van de casus in **hoofdstuk 6** tenslotte, is om niet blind een uitslag te vertrouwen. Dit geldt niet alleen voor een MoCA-score, zoals in voorgaande hoofdstukken

beargumenteerd, maar ook voor de valproïnezuur spiegel. Volgens vele (internationale) richtlijnen wordt de totale valproïnezuur concentratie gerapporteerd vanuit het laboratorium, maar niet de eigenlijk farmacologische werkzame vrije concentratie. In hoofdstuk 6 worden situaties besproken waarin deze vrije concentratie (fors) toeneemt, terwijl de totale concentratie gelijk blijft. De behandelaar kan zodoende door onvolledige informatie en onwetendheid op het verkeerde been worden gezet. Onopgemerkte cognitieve bijwerkingen van valproïnezuur kunnen dan toegeschreven worden aan andere oorzaken, zoals de hoge leeftijd. Wanneer de behandelaar in het bezit is van cognitieve uitgangswaarden – zoals te verkrijgen middels de MoCA-, kan het verval in cognitief functioneren dat veroorzaakt wordt door een valproïnezuur vergiftiging, sneller worden opgemerkt.

Conclusie:

In dit proefschrift worden argumenten aangedragen dat het van belang is om 'unseen impairment' zichtbaar te maken omdat deze negatieve invloed hebben op de kwaliteit van zorg en leven. Dit geldt in de Ouderenpsychiatrie in het bijzonder voor cognitieve stoornissen, daar deze populatie een verhoogd risico hierop loopt. Niet alleen door hoge leeftijd, maar ook gebruik van psychofarmaca en psychiatrische beelden die vaak gepaard kunnen gaan met cognitieve klachten. Hierbij kan de MoCA op meerdere manieren een positieve bijdrage leveren. 1. Door te *triageren* bij cognitieve klachten wie geen verder uitgebreid cognitief vervolg onderzoek nodig heeft en zo vele onnodige verwijzingen te voorkomen. 2. Door te *screenen*, daar de MoCA gevoelig is om onopgemerkte milde cognitieve stoornissen op te sporen. 3. Door laagdrempelig *uitgangswaarden* te verkrijgen om zo sneller cognitieve veranderingen op te merken bij een populatie met verhoogd risico, zoals patiënten in de Ouderenpsychiatrie. Of deze nu door leeftijd, toename van een psychiatrische ziekte of door bijwerkingen worden veroorzaakt.

Samengevat:

If your MMSE score is wrong, then something is really going on.
If your MoCA score is right, then you should be alright.
If your MoCA score is so so, active monitoring is the way to go.
If your MoCA score is low, an elaborate assessment should follow.

Dus....

Trust me, I am a validated test.....?
Trust me I 'm a doctor, and know how to use a validated test!

APPENDIX

Tabel 1. Conversie Tabel voor ernst indeling cognitieve stoornissen.

Mate van ernst gecategoriseerd en conversie tussen verschillende benamingen van schalen en methoden								
Methode/ uitgangspunt	*__ADL/IADL__ inschatting (mbv patiënten en vooral mantelzorgers) door behandelaar	__CDR*__ Clinical Dementia Rating Scale 1982	__GDS*__ Global Deterioration Scale Reisberg, et al. 1982	*Woorden Cog Impairment/ stoornis:	*beschrijvend	*Decline/ achteruitgang	Profiel Onderzoeksgroep In dit proefschrift	NPO's beschrijving
	Geen klachten	0	1	No Cog. Imp	No objective complains	no	**4** gezond, geen verhoogd risico **3b** verhoogd risico, niet verdacht.	Geen
	Vergeetachtig; Leeftijd gerelateerd. Cognitive impairment objectified but in accordance with age and education, although questionable.		2 age associated	Minor CI	not (jet) fulfilling the MCI criteria	Very mild/zeer lichte	**3a** verhoogd risico, verdacht en met max. lichte symptomen (geen eenduidige afwijkingen)	Geen noemenswaardige afwijkingen. Ontkrachting van cognitieve afwijkingen
.	**Hinderlijk**; Preserved independence in functional abilities. Minimale beperkingen op IADL, geen voor ADL (Winblad et al. 2004). Alles kan nog met aanpassingen, maar duidelijk minder dan voorheen .	0.5 very mild Dementia. *Probleem is dat alhier het al dementia is terwijl dit een exclusie criterium is voor MCI*	3 MCI	Mild CI	MCI, Questionable dementia	Mild/ lichte	**2a/2b**: Objectiveerbare Aanwijzing resp: Neurodegeneratief of Psychiatrie i.e.z	Objectiveerbare afwijkingen worden benoemd, kan op meer dan één domein zijn. Verminderd of afwijkend. Geen van de domeinen is -2SD = stoornis

Mate van ernst gecategoriseerd en conversie tussen verschillende benamingen van schalen en methoden								
	Beperkend; er moeten dingen worden opgegeven/ overgedragen/kan nog thuis functioneren met hulp voor IADL	1 mild D	4 Mild D	Moderate CI	Early-stage dementia	Moderate/ matige	**1** dementie	Er wordt duidelijk zonder twijfel over waarschijnlijk/ beginnende/ milde dementie gesproken passend/ voor ...dementie. Minimaal 1 keer een "stoornis" in 1 van de domeinen, Bij mogelijk/ aanwijzingen/ beginnende/ lichte/ milde is het toch groep 2a/(b).
	(zonder hulp geeft) **Problemen**. Hulp behoevend/ kan nog thuis met (veel) hulp voor ADL/	2 Moderate D	5 Moderate D	Severe	Mid-stage dementia	Moderate severe/ matig ernstige	**1** dementie	Er worden op meerdere domeinen (ernstige) stoornissen gevonden.
	(ook met hulp), **Problemen**. kan niet (goed) meer thuis verblijven. (zonder hulp zelfs **Gevaarlijk)**	3 Severe D	6 Moderate Severe	profound	Mid-stage dementia	Severe/ ernstige	**0** Dementie, geen diagnostische vraag/ verwijzing	geen
	ook met hulp **Gevaarlijk** voor gezondheid en omgeving**.**		7 Severe D	extreme	late-stage dementia, stupor	Very severe/ zeer ernstige		

*er is in deze kolom zowel de originele Engelse terminologie gebruikt als ook de Nederlandse om vertaal nuances te voorkomen.

Tabel 8.1 Conversie Tabel voor ernst indeling cognitieve stoornissen.

LIST OF PUBLICATIONS:

- The Montreal Cognitive Assessment (MoCA) with a double threshold: improving the MoCA for triaging patients in need of a neuropsychological assessment. Géraud Dautzenberg, Jeroen Lijmer, Aartjan Beekman. International Psychogeriatrics 2022 Jun;34(6):571-583. doi:10.1017/S1041610221000612

- Clinical value of the Montreal Cognitive Assessment (MoCA) in patients suspected of cognitive impairment in old age psychiatry. Using the MoCA for triaging to a memory clinic. Géraud Dautzenberg, Jeroen Lijmer, Aartjan Beekman. Cognitive Neuropsychiatry 2021 Jan;26(1):1-17. doi: 10.1080/13546805.2020.1850434

- Diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) for cognitive screening in old age psychiatry: determining cut-off scores in clinical practice. Avoiding spectrum-bias caused by healthy controls. Géraud Dautzenberg, Jeroen Lijmer, Aartjan Beekman. International Journal of Geriatric Psychiatry 2020 Mar;35(3):261-269. doi: 10.1002/gps.5227

- Severe cognitive impairment associated with a high free, but therapeutic total concentration of valproic acid due to hypoalbuminemia in an older patient with bipolar disorder. Géraud Dautzenberg*, Mariëtte Nederlof*, Aartjan Beekman, Toine Egberts, Eibert R Heerdink. * Shared first authorship. Journal of Clinical Psychopharmacology 2018 Jun;38(3):265-268. doi: 10.1097/JCP.0000000000000872.

- The Care Needs of Older Patients with Bipolar Disorder. Géraud Dautzenberg, Luuk Lans, Paul D. Meesters, Ralph Kupka, Aartjan Beekman, Max L.Stek, Annemiek Dols. Aging & Mental Health 2016 Sep;20(9):899-907. doi: 10.1080/13607863.2015.1047321

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- Play, social exploration and locomoter behavior in rats with neonatal ventral hippocampal lesions. E.W.P.M.Daenen, G.M.F.C.Dautzenberg, G.Wolterink, J.M.van Ree. Neuroscience research communications 1997 20(3),p.181.

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- Influence of amino acids of a carrier protein flanking an inserted T-cell determinant on T-cell stimulation. R.Janssen, G.Dautzenberg, J. Tommassen, W.Hoekstra. Chapter 3 in phoE of E.coli as a carrier for foreing T-cell epitopes, june1995.

Master thesis list under supervision of the autor using the same MoCA database:

Validation of the Dutch version of the Montreal Cognitive assessment in a geriatric psychiatry setting. By Wanisha Latchmansing, Master thesis 2016 Faculty of social science, Department Clinical and Health Psychology, Utrecht University

Cagla Celik, Master thesis 2016 Faculty of social science, Department Clinical and Health Psychology, Utrecht University

The effect of routine based screening (MoCA) for cognitive disorders on the healthcare for elderly. By Sarah Rooijackers. Master thesis 2017 Faculty of social science, Department Clinical and Health Psychology, Utrecht University

Validation study of the Dutch Montreal Cognitive Assessment (MoCA): A test to detect Mild Cognitive Impairment (MCI). By Mariam Shanurkeyl. Master thesis 2017. Faculty of social sciences, Department Clinical and Health Psychology, Utrecht University

Detecting differences between MCI patients with a psychiatric diagnosis and patients with a neurodegenerative diagnosis using The Montreal Cognitive. By Ilse Geurts. Master thesis 2018. Faculty of social sciences, Department Clinical and Health Psychology, Utrecht University

Dutch Depressed Elderly and Performance on the Montreal Cognitive Assessment: an Outpatient Study. By Andrea Hagg-Koelewijn. Master thesis 2018. Faculty of social sciences, Department Clinical and Health Psychology, Utrecht University

Montreal Cognitive Assessment (MoCA): Performance Comparison of Alzheimer's Disease and Vascular Dementia Patients. Master thesis 2019, by Veerle van Meijl. Department of Clinical Neuropsychology Vrije Universiteit Amsterdam

ACKNOWLEDGEMENTS – DANKWOORD

Prof.dr. A.F.T. Beekman.

Beste Aartjan, waar een gedeelde taxi rit toe kan leiden, hadden we toen niet kunnen bevroeden. Het schijnt een soort 'elevator pitch' te zijn geweest. Hoewel de rit begon bij het Museum of Art in Philadelphia tijdens (.. sorry naar) de APA, blijkt hij uiteindelijk helemaal tot hier te hebben geleid. Het begin was nog een beetje hobbelig: zoeken naar de juist weg en cadans (die taxi rit natuurlijk!). Als buitenpromovendus hoort het er een beetje bij dat je niet op een rijdende trein kunt springen. Soms leek het echter alsof ik ook het wiel opnieuw moest uitvinden. De situaties in kwestie herkende je feilloos. Je hebt me steeds aan de juiste mensen binnen je netwerk kunnen koppelen, om van hun ervaring te profiteren. Toch: zelf de route (kunnen) plannen is ook onderdeel van de reis (die een promovendus maakt) en dit draagt ook bij aan de intrinsieke motivatie om bij zo'n lang traject het oog op de horizon te kunnen houden. Jij bent hierbij mijn kompas gebleken. Niet zelden heb je me 'back on track' gezet als ik dreigde af te dwalen naar zijsporen. Dit deed je op een manier waarbij je me ogenschijnlijk zelf de keuzes liet maken, maar daarbij me duidelijk (probeerde) maakte dat er een focus moest zijn, of wat mijn focus moest zijn. Een psychiater zou deze manier misschien als narcistisch sparend kunnen duiden, maar ik vond het zeer prettig en stimulerend (wacht… ik zou toch niet…!? ,…). Het blijft een uitdaging om zelf in de periferie een onderwerp vorm te geven en dat dan weten te vertalen naar een onderzoeksopzet. Echter, onderzoek doen vanuit de klinische praktijk maakte me ook heel enthousiast, maar daardoor zag ik de valkuilen niet altijd (meer). Hierin liet je me leren maar bewaakte je goed de wetenschappelijke kaders. Mede doordat mijn onderzoek was ontstaan vanuit mijn dagelijkse werk en uitgevoerd in de periferie, is misschien het geen 'diep' (*hoog-specialistisch*) onderzoek geworden. Maar het is in mijn ogen echter wel 'breed' toepasbaar in, en daarmee ook van belang voor, de ouderenpsychiatrie. Dank dat je dit onderzoeksonderwerp hebt gesteund; genoeg promotoren zouden het niet uitdagend genoeg hebben gevonden. De uitdaging lag in dit (of mijn) geval meer in het begeleiden van de buitenpromovendus vermoed ik en bij het op de juiste wijze verzamelen van alle data. Ik wil je hartelijk danken voor het vertrouwen dat je in me had, mede waardoor ik deze mooie reis heb mogen maken.

Dr. J.G. Lijmer. Beste Jeroen, over (trein)reizen gesproken…wij leggen al sinds onze opleiding in het AZU (UMCU) veel trajecten samen af. Hoewel jij wel steeds een paar wagons voor me zit. Dank dat je me hebt willen ondersteunen op deze reis (…..en ook het onderzoek). Hoewel je zou kunnen zeggen dat jij je, in mijn geval, bij een al rijdende trein hebt gevoegd

(qua onderzoeksonderwerp en ontwerp), was mijn situatie meer een op gang komende stoomlocomotief die nog op het rangeer terrein stond. Ik wist waar ik heen wilde en welke wagonnetjes ik wilde meenemen. Maar hoe bij het eindstation te komen met die wirwar aan sporen, zonder op een dood spoor te geraken, is mede aan jou te danken. Op vele momenten stond je naast me, zoals bij de presentaties van onze resultaten op congressen (van Vancouver tot aan bij jou thuis voor online presentaties ivm COVID-19 restricties). Je nam altijd de tijd ook na een pittige congres dag, waar ik nogal eens klaar was met de wetenschap. Maar na gedane arbeid, was er ook tijd voor ontspanning en ontdekking! Je wist altijd de meest verstopte en cultureel interessante plekjes te vinden (we zwijgen maar even over het inline dancen in Japan en al helemaal over Cinco de Mayo in DC). Je bent niet alleen voor de wetenschap een (co-)promotor voor mij geweest, maar ook privé. Je hebt me leren genieten van voor mij onbekende dingen (vooruit, niet alle jazz) en ook hoe. Je hebt een tomeloze energie, en evenzoveel honger naar kennis maar ook een drukke agenda (hoeveel kinderen had je ook al weer?). Daarom: nogmaals dank dat je tijd heb gemaakt. Deze trein is bij zijn eindhalte aangekomen, maar onze reizen samen nog niet!

Dr. H.C. Comijs. Beste Hannie, de trein is een thema, naar het zich laat aanzien. Vaak hebben wij in de stationsrestauratie van Utrecht Centraal afgesproken. Jij op weg naar huis, toch nog tijd vrijmakend voor mij. Ik wil je hartelijk danken voor je begeleiding, ook al hebben we (door je vervroegd pensioen, of duurde mijn onderzoek echt zo lang?) deze reis niet samen uitgereden. Maar je hebt me goed op weg geholpen. Zonder jouw hulp om de professionele slag te maken, en daarbij de wettelijke kaders niet uit het zicht te verliezen, was het mij niet gelukt. Ik heb veel van je mogen leren over hoe een onderzoek op te zetten. Maar ook wees je me erop dat werk niet (alles) moet overheersen: bedankt hiervoor.

Leden van de beoordelingscommissie (en oppositiecommissie): prof.dr. R.W. (Ralph) Kupka, prof. dr. A.W. (Arjan) Braam, prof.dr. H.C. (Henry) Weinstein, prof.dr. W. (Wiepke) Cahn, dr. C.R. (Linda) Tulner en dr. A. (Annemieke) Dols. Ik weet dat ik het jullie er niet gemakkelijker op heb gemaakt met mijn manuscript. Daarom is mijn dank zo mogelijk nog groter voor de tijd en de moeite die jullie hebben genomen om mijn proefschrift zeer gedetailleerd door te nemen en van commentaar te voorzien. Sommigen van jullie ben ik reeds tegengekomen op cruciale kruisingen in mijn leven, waar jullie me hebben helpen oversteken. Anderen zie ik voor het eerst bij de verdediging. Wiepke, je was de gemoedelijke en toegankelijke supervisor tijdens de (basis)opleiding tot psychiater voor de assistenten, maar ook voor de patiënten op de afdeling. Zoals je ons leerde de mens achter de patiënt te zien, zag jij die mens ook in de assistent. Ik heb daar nog steeds goede herinneringen aan.

Ralph, jij werd mijn (tijdelijke) opleider, toen ik vanuit het AZU sociale psychiatrie moest (ok, ging) 'lopen' bij Atrecht. Ik was getraind in spiegels, scorelijsten, protocollen en uitzonderingen. Maar crisisdiensten, huisbezoeken (of zoektochtjes onder een brug…), de sociale psychiatrie zeg maar, was nieuw (lees: eng) voor me. Je hebt me snel hierin wegwijs kunnen maken.
Arjan, ook jou ben ik op een kruispunt tegen gekomen. Zij het in privé omstandigheden. Dat onze kleine meisjes van die echo nu al zo groot zijn. Later heb ik van jou als opleider bij Altrecht nog veel over (sociale)psychiatrie kunnen leren. Ook al was ik 'al psychiater' ik was zeker nog niet uitgeleerd.
Annemieke, voor mijn eerste artikel heb ik jullie data mogen gebruiken. Dank voor het vertrouwen. Ook heb ik veel van je geleerd hoe je passie met efficiëntie moet blijven combineren. Ook jij moest me leren om van de zijsporen weg te blijven, waar ik soms vol passie naar toe was gestoomd.
Met groot respect zie ik uit naar de kennismaking met prof.dr. Weinstein, dr. Tulner en dr. van Exel. Aan jullie staat van dienst te zien, zal het een uitdagend moment voor mij worden. Ook zal dit moment, hoe het ook zal verlopen, achteraf een kruispunt blijken dat ik over heb gestoken en waar jullie een rol in hebben gespeeld.

Co-auteurs: Luuk (SPSS); Paul David (statistiek); Ralph (mentor); Max (doel); Annemiek (data); Mariëtte (precies); Rob (overzicht); Toine (rust). Zonder jullie medewerking, deskundigheid en tijd waren de respectievelijke artikelen niet van de grond gekomen en daarmee dit proefschrift. Dank voor het vertrouwen. Het lijkt inderdaad goed te zijn gekomen.

De 'data queen' studenten en 'data king' Kasper van Mens voor data. De (neuro)psychologie studenten van de UU en VU. Zonder jullie zat ik nu waarschijnlijk nog de MoCA's in Excel in te voeren en naar SPSS te staren. Maar meer nog dan hulp bieden bij het invoeren van de data, hebben jullie me bij de les gehouden door jullie onophoudelijke stroom vragen. Daardoor moest ik zaken ook voor mijzelf goed ordenen. Dank! Kasper, zonder jouw toverkunsten zouden al die MoCA's alleen maar getallen zijn (of te wel kwantitatief, H1 lees maar). Door jou konden de MoCA's in de context geplaatst worden bij de meer dan 10.000 patiënten van wie jij me van zoveel data voorzag. En als ik tussen al die ééntjes en nulletjes de patiënten niet meer zag, was je er altijd om me rustig de betekenissen uit te leggen, of me van een nieuw databestand te voorzien. Hiermee kon het kwalitatieve kader geschapen worden.

De taalpolitie: Jamie (you are a native speaker, but I can't understand a thing you say) Maïlis (transforming rock-cabbage into medical English), Sophie (keep it simple, stupid),

Caroline (wat wil je nou eigenlijk zeggen? Hou het simpel, slimmerd), abstract king- Ruud en Jo-Anneke (niet te kunstzinnig graag). Dank voor jullie tijd!

De Commissie wetenschappelijk onderzoek (CWO) van Altrecht wil ik danken voor de begeleiding en het geduld. Hierbij wil ik expliciet Carieneke en Marian noemen. Maar ook Eline wil ik bedanken voor de mogelijkheid om altijd aan te kloppen met vragen, om te sparren en om te klagen. Jammer dat het er (nog) niet van gekomen is om onze ideeën in een onderzoek om te zetten. Ik heb nu weer tijd…jij?

Not last and certainly not least wil ik de proefpersonen bedanken. De vele anonieme patiënten wiens data we hebben mogen gebruiken. De ruim 1600 patiënten die allemaal de MoCA hebben ondergaan, terwijl deze in de begin jaren nog niet gebruikelijk was. De 100 patiënten die de tijd vrij hebben gemaakt om nogmaals door de cognitieve molen te gaan voor het longitudinale onderzoek. De gezonde vrijwilligers, die de gezonde controle groep vormden, en die hun tijd gaven. Maar ook de specifieke patiënten wiens MoCA afname we op video anoniem mochten vastleggen voor trainingsdoeleinden en interbeoordelaars variabiliteit. In het bijzonder wil ik graag de patiënte en haar naasten uit hoofdstuk 6 bedanken. Ondanks dat er een zeer ernstige situatie door mij was veroorzaakt, wilden zij meewerken aan dit artikel of liever, eisten zij dit bijna. Dank voor het vertrouwen dat in mij is gesteld.

Lia en Peter wil ik ook graag hier bedanken. Zonder jullie was deze reis niet mogelijk geweest. Jullie hebben ingestemd met mijn wensen toen ik solliciteerde. Hoewel ik geduldig heb moeten wachten op mijn beurt vooraleer ik mocht starten met mijn promotietraject, hebben jullie het einde hiervan helaas niet meer als directe collegae bij Atrecht mogen meemaken. Heeft het traject dan echt zo lang geduurd? Alex en Lotte, jullie zaten met een contract en nog geen tastbaar resultaat toen jullie in functie kwamen. Maar het *gentlemen agreement* heeft zich gehouden. Dank aan jullie voor het gestelde vertrouwen.

Mijn teammanagers: van Moos - met velen er soms tijdelijk tussenin waaronder Krista - - naar Monique en Mijke (en weer terug naar Monique?). Dank voor de steun en voor het creëren van omstandigheden op de werkvloer die dit traject mogelijk maakten. Moos, jou wil ik in het bijzonder bedanken voor je betrokkenheid en inzet over de vele jaren. Voor je creativiteit als teammanager om niet alleen mijn klinische werk te faciliteren, maar om ook een warm en aangenaam werkklimaat te faciliteren. Tevens heb je je ingezet om een prettige (en functionele) onderzoektijd te scheppen. Niet alleen voor mij, maar ook voor studenten en een AIOS, door stagevergoedingen te regelen en een prettige re-integratie plek te bieden.

Natuurlijk zou ik dit onderzoek niet hebben kunnen doen zonder de steun en waarneming van en door mijn collegae psychiaters en klinisch geriaters. Velen zijn er geweest, sommigen zijn gebleven, maar allen hebben aan dit proefschrift bijgedragen. Van Rob (in het prille begin: je was een voorbeeld dat promoveren kán in de periferie) en Joost (je begeleidde me in de praktische zaken van onderzoek doen), via Rozemarijn en Nico (dank voor het helpen met de figuren) naar 'nieuweling' Addy (terwijl ik ooit AGNIO bij je was!). Dank voor al jullie tijd en geduld. Maar één collega wil ik in het bijzonder noemen. Ellemieke, samen zijn we begonnen bij ouderen en hebben we veel vernieuwingen (verbeteringen, vinden wij) geïntroduceerd. Mede door de gestroomlijnde intakestraatjes kon de MoCA afname zo makkelijk gestandaardiseerd worden dat het voor het onderzoek bruikbaar was. Maar niet alleen heb je bijgedragen via het organiseren en waarnemen (de hardware zeg maar) maar ook door oog te hebben voor de software die daarachter draaide. Gelukkig mogen we nog 17 jaar samenwerken, het zit bijna erop.

Van Rinus, Maria, Ellen, Maaike, Hennie, Jaap, Judith, Anne, Lea, Tom, Vincent, Jacqueline, etc etc tot aan het huidige team van SPVers (en casemanagers), waaronder 'jonkie' Anja die wél nog naar me luistert. Hoewel jullie vaak gevraagd wordt de zoveelste vragenlijst af te nemen bij de patiënten, had ik het gevoel dat de weerstand tegen de MoCA er niet of in ieder geval in geringe mate was. Dit gaf mij de overtuiging dat mijn onderzoek vanuit de praktijk gedragen werd en als zinvol werd ervaren. Er was gezonde weerstand, 'ja ja nu weten we het wel', tegen mijn gehamer hoe de MoCA afgenomen diende te worden. Ik ben jullie zeer dankbaar voor al die duizenden MoCA's die zijn afgenomen. Helaas heb ik nu aangetoond dat de MoCA zin heeft, dus jullie komen er niet meer vanaf!

Zonder secretaresses zouden al die MoCA testen niet bij de intakeformulieren of in het archief terecht zijn gekomen. Van Wil en Petra, via Inge en Mariëlle, naar het huidige team van het ZA en velen er tussen in. Dank voor jullie begrip en preciesie. Julie mogen nu stoppen met archiveren. Wel liggen er dankzij jullie nog meer dan 1000 MoCA's te wachten om gedigitaliseerd te worden. Wie wil?

De werknemers van de geheugenpoli's wil ik ook bedanken. De vele collegae van verschillende vakgroepen (neurologie, geriatrie, psychologie, RPCW, Mesos) met even zo veel meningen. Maar van al die meningen over MRI's, NPO's en wat al niet meer zij, profiteerden niet alleen de patiënten, maar ook ik. Ik heb geleerd naar andere invalshoeken te kunnen luisteren. In het bijzonder wil ik Hanneke noemen. Jouw inzet om samen de GP Woerden vorm te geven en te professionaliseren was inspirerend. Ook wil ik Caroline bedanken voor de hulp bij het opzetten van de GP -West. Zonder jouw ervaring, meedenken en stroomlijnen zou de poli zijn doel voorbij zijn geschoten.

De psychologen: jullie weerstand tegen de MoCA ('want deze is niet gevalideerd in het Nederlands') was ongekend...Nou, hier is ie dan! Nee, zonder gekheid: dank ben ik aan velen van jullie verschuldigd (Tim, Petra, Monique, Gerard etc., maar met een aantal heb ik vaker over testen, betekenissen en de interpretaties hiervan gesproken. Dus ook al leer ik van jullie allen, graag wil ik specifiek Bernadette, Carien (en Caroline, maar nu weet ze het wel) hiervoor bedanken.

De gedachteslijpers van PAN, met in het bijzonder Simon B. Zonder de eeuwige jeugd die aan een dispuut verbonden is, zou ik als digibeet nu nog steeds mijn data zonder Excel aan het ordenen zijn. De tweewekelijkse lezingavonden blijven me verrijken met kennis. Is het niet over studieonderwerpen, dan is het wel over het ‚studentenleven van tegenwoordig. Daarnaast is het natuurlijk fijn om met mijn generatiegenoten af en toe te mijmeren over ('ons') vroeger, toen gelukkig nog veel analoog ging. Hoe prettig om elkaars expertise* nu te kunnen misbruiken, en het gezeur te weerleggen van generaties boven ons, die beweren dat alles vroeger beter was.
*PS: als het zover is en jullie niet meer weten hoe een telefoon werkt (of mij niet meer herinneren), mag je me bellen; dan neem ik de MoCA af. Kan ik ook eens wat terug doen.

J.C. C. d'O wil ik bedanken. Hoewel... wat hebben jullie überhaupt bijgedragen dat jullie moeten worden bedankt, buiten het gegeven dat dit proefschrift door jullie mogelijk nog langer op zich heeft laten wachten?

Hierbij wil ik natuurlijk een ieder bedanken die hierboven gezocht heeft naar zijn of haar naam en die (nog) niet gevonden heeft. Je bijdrage was onvergetelijk.

Zo, dan zijn we nu aangekomen bij de vrienden en familieleden die echt helemaal niets aan dit proefschrift hebben bijgedragen. Ook niet in negatieve zin. En daar wil ik jullie hartelijk voor bedanken! Bart, Hanneke, Jan-Jaap, Jeroen, José, Judith, Marieke, Martijn, Michiel, Nicole, Olivier, Ronald, Stanley, Teuntje, Yulia, WeiLie, etc..

Speurneusjes: ik leg jullie achteraf nog wel eens uit hoe cognitieve achteruitgang ontstaat, als het dan niet al te laat is. Voor nu, dank voor de fijne oplaadmomenten.

Lieve Else: zo, nu ben ik ook klaar. Kunnen we weer zoals vroeger gaan mijmeren over Jung, maar nu waarschijnlijk ook over oud. Waarheen is de tijd gegaan?

Eugénie & Sixte: de vele discussies aan de ontbijttafel hebben er waarschijnlijk voor gezorgd dat ik zo ben geworden zoals ik nu ben. Een kritisch doorvrager, bedoel ik, *niet a pain in the* ... Het was uiteindelijk waardevol. Dank dat jullie er waren, zeker ook in de moeilijke tijden.

Bü: 'Ehre ist eine wichtige Eigenschaft, aber Stolz sollte niemals der Vernunft im Wege stehen'. Danke für die vielen Lebenslektionen. Du hast viele erleben müssen.

Jan & Lenie, Marieke. Schoonfamiliegrappen zijn er vast niet voor niets. Ik snap ze alleen nog niet. Misschien komt dat ook doordat jullie me hartelijk hebben opgenomen in de familie en ik zo toch bij de warme kant ben gaan horen.

Ab: hoe jij tot op hoge (excuus, rijpe) leeftijd nog steeds met publicaties bezig bent, is inspirerend. Hoewel ik niet weet of ik het ambieer om net zo lang door te werken als jij. Ik hoop wél dat ik - net als jij- zo bevlogen kan zijn van een onderwerp dat het niet als werken aanvoelt. Ik ben dankbaar dat je in ons leven bent gekomen. Onze periodes in Menton, heerlijk aan zee, allebei schavend aan een artikel, met soms een zucht van een van ons, geven me nog steeds een warm gevoel.

Pap, toen ik ging studeren gaf je me één advies: "*Studeer zo lang mogelijk. Maar zorg dat je niet de laatste bent*". Heb ik dit te letterlijk genomen en bedoelde je niet *lang* maar *veel*? Ach, ik heb het niet van een vreemde. Hoe dan ook, dank voor alle steun en voor de vanzelfsprekendheid dat je dit proces hebt mogelijk gemaakt. Ook al maak je het hoogtepunt niet meer mee, de weg ernaartoe hebben we samen kunnen bewandelen. Je bent een inspiratie in al je doen én laten.

Mam, ook al was onze gezamenlijke reis (te) kort, je heb me al jong wat statistiek bijgebracht. *Wees jezelf, ook al is dat mainstream.* Of omgekeerd: *wees alleen gemiddeld als je dat ook echt bent*. Ik probeer het.

Mijn goudenbergjes: Hebe & Caïssa: jullie hebben mijn leven verrijkt. Ik heb zo veel van en door jullie geleerd en zal nog veel meer van jullie gaan leren. Ik verheug me op onze verdere reis samen en jullie kritische vragen en opmerkingen. Jantine, voorgaande geldt ook voor jou (behalve dat laatste dan, maar daar werk ik aan!). Dank voor je morele steun! Nu kan jij weer aan de bak! Of moet het zijn 'nu mag ik weer'!

Mijn paranimfen, Camille en Gordon. Was soll ich denn jetzt sagen? Julie vergezellen mij al sinds de middelbare school op mijn reis, excuus *onze* reis. We hebben vele bergen beklommen (met soms wat moeizame afdalingen zoals in Tanzania) en dalen doorkruist. We verstaan elkaars gegrom (meestal) en hebben daar ook genoeg aan want we kennen elkaar door en door (denk ik, maar daar praten we niet over, heuheuheu). Noe weess ech uht sécher,..... deess gemeinsam rees geeht neet naar Denemarke, mä an d'Zukunft. Dës Rees ass nach laang net fäerdeg a mir maachen de Rescht zesummen!

ABOUT THE AUTHOR

Géraud grew up in Luxembourg. His first steps in the world of acquiring knowledge were taken at the garderie Luxembourg and the Ecole Eurpéene Luxembourg. Partly due to being diagnosed with dyslexia, his school career continued in the Netherlands at the Episcopal boarding school (Bisschoppelijk college). Here, where they were seemingly more advanced in how to approach dyslexia, the Atheneum was completed.

In 1990, he started Biology at Utrecht University. This was followed by studying History of Art in 1993 and Medicine in 1994, both at the same university. In 1996, the master in Biology was obtained with specializations in molecular biology (Vakgroep Moleculaire Microbiologie 1993-1994, under supervision of prof.dr. Wiel Hoekstra) and Neuroethology (Rudolf Magnus Instituut voor Neurowetenschappen, Utrecht,1995-1996, prof.dr. Jan van Ree).

His master thesis in Biology was titled *Neglect; no, one, or many circuits*. Under supervision of prof dr. Jan van Ree and prof.dr. Edward de Haan.

Furthermore, in 1998 the masters in Medicine was obtained with a thesis on an fMRI study of synesthesia under supervision of prof.dr. Margiet Sitskoorn.

Géraud continued Medical school with internships at Harvard (Boston), Kings College (London), 's Lands Hospital (Paramaribo) together with internships at Komfo Anokye Teaching Hospital, Ghana and Bangkok.

After his MD degree in 2000, residencies in Neurology and later Psychiatry were followed. In 2006 under supervision of prof.dr. René Kahn, he graduated from his psychiatry residency program at the teaching hospital of the Utrecht University (AZU/UMCU). With focus on Acquired brain injury (Vesalius) and old age psychiatry (Jeroen Bosch Ziekenhuis).

In 2006 Géraud started working (and still is up to this day) as an old age psychiatrist at Altrecht, Utrecht, with focus on cognitive impairment and bipolar disorders. He was engaged in developing two memory clinics in the region of Utrecht, where he worked until 2016. In 2021 he joined as a consultant at a new supra regional specialised dementia ward (D-ZEP; Dementie- en Zeer Ernstig Probleemgedrag).

Next to his work as an old age psychiatrist Géraud is also involved in the start-up of Cupplement (coffee with supplements supporting better health www.drinkcupplement.com) and Play to Work (gamified recruitment assessments www.playtowork.nl).

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