Reflections on clinical neuropsychology

A multifaceted approach

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Cover design: HSP Reclame en Communicatie, Dennis van den Broek
Layout: Nicole Nijhuis - Gildeprint
Printed by: Gildeprint - Enschede
ISBN: 978-90-393-6113-9

Reflections on clinical neuropsychology

A multifaceted approach

Een veelzijdige benadering van de klinische neuropsychologie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 11 april 2014 des middags om 12.45 uur

door

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geboren 1 december 1980
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Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van Alzheimer Nederland, Internationale Stichting Alzheimer Onderzoek, Novo Nordisk B.V., Science Plus Group B.V. en Metrisquare Europe GmbH.

Contents

De tijd gaat voorbij zeggen we, maar we vergissen ons,
de tijd blijft en wij zijn het die voorbij gaan.

Raspail

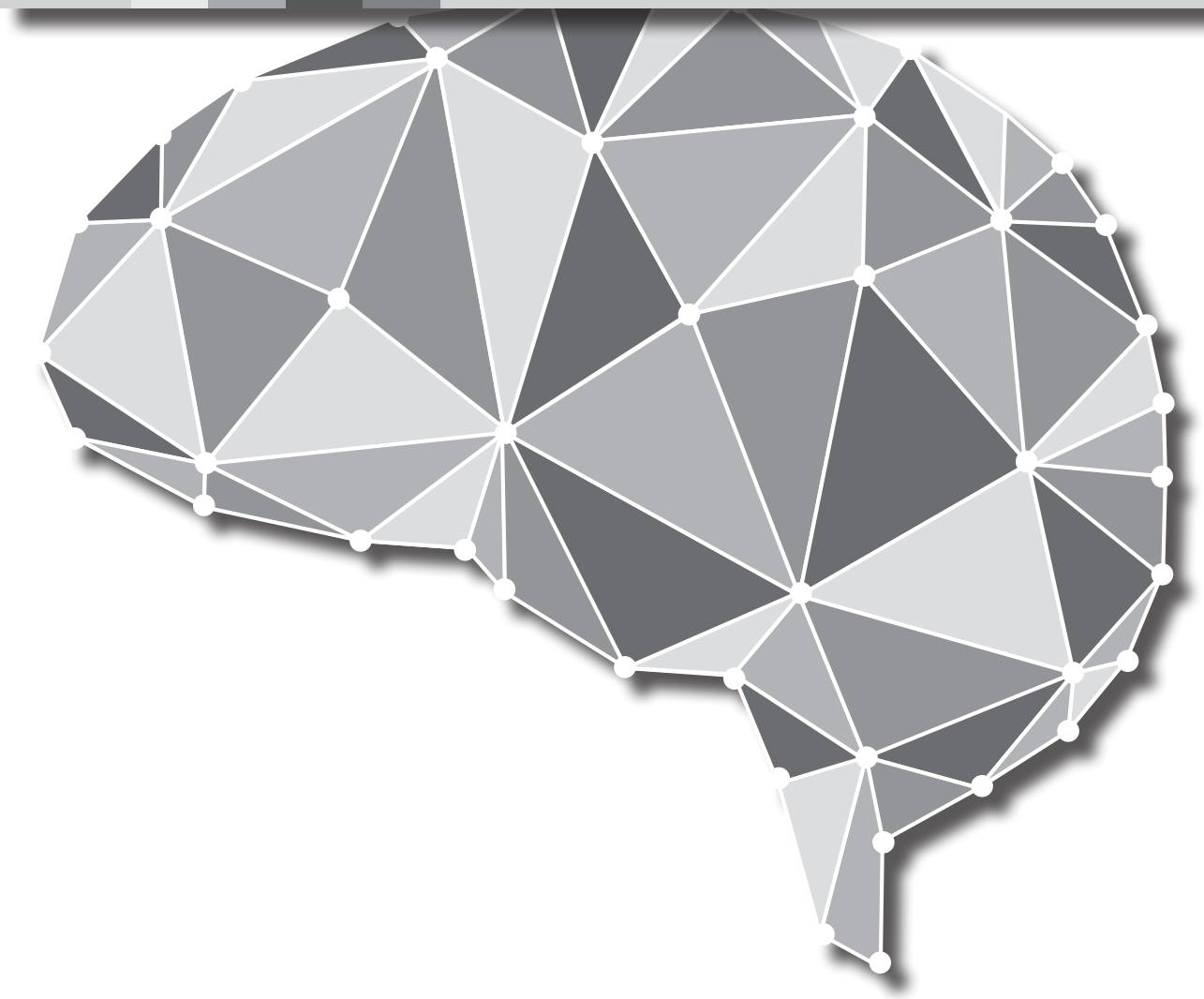
Voor mijn opa's

Foreword

In my work as a neuropsychologist at the University Medical Centre Utrecht and Utrecht University, I am constantly in touch with different aspects of the field. These aspects vary from diagnosis to treatment and from patient care to research. The variety in my work stimulates and challenges me, but also confronts me with critical questions. Those questions form the basis of this thesis and they reflect my interests in both clinical care as well as in research. I will describe a variety of studies, such as epidemiological studies, case reports, clinical trials, quantitative research and qualitative studies. This thesis is a reflection on my work over the past several years.

CHAPTER 1

General introduction



To put the theme of this thesis in perspective, I will start describing the history of neuropsychology and the development of the neuropsychological examination. Then, I will outline different purposes of this examination currently, and describe the frame of reference and outline of the thesis.

History of neuropsychology

Neuropsychology is described as "*an applied science concerned with the behavioural expression of brain function*" (1). As an independent discipline, neuropsychology is a relatively young science; in the Netherlands the first neuropsychology curricula started in the 1970s and 1980s (2). However, the fundamentals of this science go back much further. Many philosophers, physicians, neurologists and psychiatrists have studied the relation between brain areas and psychological functions for a long time. The famous philosopher René Descartes (1596-1650) developed one of the first important theories concerning this topic. According to his view, human beings consisted of two substances, the body and the mind. Descartes localised the mind in the middle of the head, at the pineal gland. Opposite to Descartes' view, neuroanatomist and physiologist Franz Joseph Gall (1758-1828) was not interested in the middle but rather in the outside of the brain. His theory, also known as phrenology, assumed that specific functions could be measured by studying the skull of a person (3). In later decades, patient studies became the most important tool for understanding and localising specific cognitive functions. Ground breaking new insights in language functions followed Paul Broca's (1824-1880) description of a patient called 'Tan' (4). The only word this patient could express was 'tan'; however, he was able to comprehend what was said to him. After Tan's death, Broca performed an autopsy of his brain and a lesion in the left frontal lobe was found (this area was later called Broca's area). This finding was highly important in the localisation of language functions, even as in the awareness of the dominance of the left hemisphere (5). Likewise, patient H.M. (6) taught us much about human memory. H.M. was suffering from epilepsy and at the age of twenty-seven, parts of his temporal lobes (including the hippocampus) were surgically removed to stop his epileptic insults. After the resection, H.M. was not able to remember new information. However, his working memory was unimpaired. These findings taught us much about the memory system and the contribution of this knowledge for neuroscience was enormous (7). After a period wherein localising functions were most important, a contrary more holistic view of the brain was adapted (8). In turn, Aleksandr Luria (1902-1977), a Russian neuropsychologist, was one of the first who combined a holistic and a localisation perspective. According to his view the brain is one complex functional system, in which multiple subsystems exist.

After attaining more knowledge about cognitive functions, the need to measure these functions was growing. During the twentieth century, several intelligence scales were developed, initially as a selection procedure for soldiers in the army. One of them was the Wechsler Adult Intelligence Scale, of which the first version was developed in 1939 (9). At the same time, several neuropsychological tests were developed, such as the Stroop Colour-Word Test in 1935 (10), the complex figure of Rey in 1941 (11) and the Wechsler Memory scale in 1945 (12). During the last decades of the twentieth century, several neuropsychological test batteries were developed, such as the Luria Nebraska neuropsychological battery (13), so that cognition could be systematically measured and described (8).

Neuropsychology today

Neuropsychology has currently developed into a rapidly growing, independent discipline with a broad work field. Neuropsychologists are working in many different settings, such as hospitals, rehabilitation centres, nursing homes, forensic organisations and research institutes. Innumerable neuropsychological tests and neuropsychological test batteries are available, measuring global cognition or very specific cognitive functions (13, 14).

Thus far, one of the most important instruments of a neuropsychologist in assessing the behavioural expression of brain functions is the neuropsychological examination. During such an examination, the neuropsychologist evokes behaviour of a patient in a controlled manner. This is done by the use of different neuropsychological tests. The neuropsychologist integrates test scores, information obtained from the interview and observations made throughout the examination, before interpreting the relation between behaviour and brain functions.

Despite myriad technical and medical developments in the last decades, the neuropsychological examination undoubtedly maintains its specific value. Whereas imaging techniques, lumbar punctures and blood investigations can be of high value in diagnostic processes, they do not tell us anything about the cognitive status of a patient. The neuropsychological examination is therefore still indispensable in answering questions about cognition.

A neuropsychological examination can be administrated with different purposes. It is used in treatment programs and in a broad scope of research projects focussing on cognition in healthy people or in patient groups. The most characteristic purpose of a neuropsychological examination is to contribute to the diagnostic process.

Purposes of a neuropsychological examination described by Lezak

In a time of rapidly developing imaging techniques, medical procedures, knowledge about cognition, and neuropsychological instruments, the need to stop and remember the fundamental purposes of our work is growing. The enormous growth and width of our profession sometimes makes it difficult to oversee the whole spectrum of purposes of a neuropsychological examination.
In one of the most important handbooks for neuropsychologists today, Lezak's "Neuropsychological Assessment" (1), an overview of different purposes of a neuropsychological examination is given. These purposes create a frame of reference for the studies composing this thesis. The different purposes are:

1. Diagnosis
2. Patient care
3. Treatment
4. Research
5. Forensic questions (mainly in the US and, to a lesser extent elsewhere)

In the subsequent paragraphs, I will describe what is meant by these purposes. Because answering forensic questions is a less prominent task of neuropsychologists in the Netherlands, and especially in my work at a university medical centre, this purpose will not be discussed.

The first purpose of a neuropsychological examination is *diagnosis*. The neuropsychological examination is used to analyse different cognitive functions and can be helpful to discriminate between different cognitive profiles referring to underlying diseases. Although imaging techniques presently also play an important role in these kinds of procedures, the neuropsychological examination is still indispensable in providing information about the kind and gravity of cognitive disorders. People with lesions in the same part of their brains can differ enormously in their cognitive profiles. Furthermore, some diseases start with cognitive deficits without any notable neurological disorders. In these patients the neuropsychological examination is of critical value in the diagnostic process.

The second purpose of a neuropsychological examination is *patient care*. Having a (neurological) disease and being confronted with several restrictions in daily life can have a huge impact on our behaviour. The neuropsychologist has the task of explaining the results of a neuropsychological assessment as comprehensive as possible so that a patient understands the possible disorders and comprehends why specific care is needed. Psychological aspects

of being ill should also be taken into account. Patients respond differently to disease and they may have unrealistic expectations for the future. Furthermore, compensating for a cognitive disorder is more feasible for some patients than for others. Clear explanations of both cognitive as psychological aspects can be helpful for a patient and his family.

The third purpose of a neuropsychological examination is *treatment*. Lezak differentiates between *treatment planning and remediation* and *treatment evaluation*. For a good treatment planning, an extensive and sensitive neuropsychological examination is needed. This examination can be helpful in determining the most appropriate treatment for a patient. In treatment evaluation, a neuropsychological examination can help to evaluate the effectiveness of a treatment program and can play a role in cost-effectiveness discussions about different kind of interventions.

The fourth purpose of a neuropsychological examination is *research*. Neuropsychological examinations are used to study the relation between brain and behaviour, both in healthy persons and in patients. Research also involves development, standardisation and evaluation of neuropsychological tests. Furthermore, tests that are primarily designated to assess normal brain functions are used more and more often in clinical care. Neuropsychological assessments can be helpful in brain mapping studies and can teach us more about the character and course of specific diseases.

Aim of this thesis

The versatility of the neuropsychological examination is not always fully realised or utilised. The aim of this thesis is to demonstrate the diversity of the purposes of a neuropsychological examination. I will do this by presenting a series of studies that—although each study was performed for its own specific goal—reflect these different purposes. We have organised the studies within the frame of reference proposed by Lezak. By describing different kinds of studies, we hope to contribute to the awareness of neuropsychologists about the fundamental purposes of our work. Being aware of the different purposes of a neuropsychological examination can be helpful in looking outside the standard boundaries of the profession. In the general discussion of this thesis, we propose a more integrated use of the different purposes and describe the benefits of combining research and clinical care.

Thesis outline

Chapter 2 and chapter 3 will describe the neuropsychological examination as a **diagnostic tool** in two case studies**.**

In **chapter 2** we describe patient GK. This patient complained about visual problems. The ophthalmologist could not find an explanation for his complaints. After three years, when GK also began to suffer from memory and concentration problems, he was referred to our memory clinic. An extensive neuropsychological assessment with a detailed examination of the visuoperception finally gave an explanation for his complaints. The visual problems were not the result of an ophthalmologic disorder, but GK was suffering from Posterior Cortical Atrophy. This study indicates that a specified neuropsychological examination can be an essential part of the diagnostic process.

In **chapter 3** we describe patient FV. This patient complained about memory and navigation problems after incidental ecstasy use. At first, his complaints were attributed to a burnout and although FV experienced persistent and serious cognitive problems, his complaints were not analysed until he visited the memory clinic seven years after the incident. The neuropsychological assessment revealed a major memory disorder. Because a standard neuropsychological assessment could not properly analyse navigation skills, we added an experimental task to our test battery. This virtual reality test indicated that FV also had major navigation problems. This study shows that the neuropsychological examination can also be valuable in the diagnostic process of less-frequently reported cognitive complaints such as navigation problems.

Chapter 4 and chapter 5 discuss different aspects of the neuropsychological examination in **patient care**.

In **chapter 4**, the use of the Symptom Checklist 90-Revised in neurological outpatients is discussed. This questionnaire is used to measure both psychiatric as well as psychosomatic complaints. The measurement of such complaints is highly important to investigate the psychological aspects of having a (neurological) disease and plays an important role in patient care. In this chapter we discuss whether such a questionnaire is applicable in a neurological outpatient group as well as the use of normative data from a healthy control group.

Chapter 5 describes the importance of being coached during awake craniotomy. During such a procedure, a patient's cognitive status is monitored. However, patients undergoing awake surgery also need psychological support. Most of the patients undergoing an awake craniotomy have just been recently diagnosed with a brain tumour. The impact of this diagnosis in combination with, for most patients, intensive and sometimes frightening situation of an awake craniotomy requires specific coaching. Optimal patient care has the highest priority in these patients. In this study we analysed patients' perceptions during the procedure. We describe what factors are, according to our patients, most important in coaching during awake craniotomy.

Chapter 6 illustrates the neuropsychological examination as a manner to evaluate **treatment**.

In this study we analyse the application of the errorless learning training program in a patient population with moderate to severe dementia. The errorless learning method is a well-defined method in overcoming memory problems. By using a spared implicit memory and by the prevention of errors, a better memory performance should be reached. The applicability of this method was just minimally tested in clinical populations and never before in patients with moderate to severe dementia. This study questions whether the errorless learning method is applicable in this kind of patient population and evaluates the effectiveness of this kind of treatment.

Chapter 7, 8 and 9 are examples of the neuropsychological examination in **research**.

In **chapter 7** the cognitive status of patients with type 2 diabetes mellitus is studied. It is known that diabetes is associated with cognitive decrements and an increased risk of dementia. Many studies have analysed these relations, but none of them studied the cognitive profile of diabetes patients in the very early stage of the disease. Patients in this study were included 3 to 4 years after they were diagnosed (by screen detection) with diabetes mellitus. This kind of study can teach us more about the course of the disease and can be helpful in understanding the underlying mechanism.

In **chapter 8** the relation between a frequently used telephonic screening instrument, the Telephone Interview for Cognitive Status (TICS) and a comprehensive neuropsychological assessment is analysed. Although frequently used, several psychometric questions about the TICS were still unanswered. When using a screening instrument, it is important to know exactly which cognitive constructs it measures and whether it reflects cognition in general or more solitary cognition functions.

Chapter 9 analyses the effect of self-reported depressive symptoms on memory function in neurological patients. From previous research, we know that a depressed mood can have negative effects on cognition. Therefore, when administrating a neuropsychological assessment in clinical care, neuropsychologists should investigate a possible depression. Usually, this is done by administrating a depression scale such as the Beck Depression Inventory (BDI). This study analyses the relation between self-reported depressive symptoms, measured by the BDI, and the performance on different memory tasks. Results of this study are important for neuropsychologists in the interpretation of neuropsychological test scores.

Chapter 10 provides the general discussion and summarises the main findings of the studies. Furthermore, it questions whether the different purposes of a neuropsychological examination should be seen as isolated aspects. A multipurpose examination, in which the different purposes are more integrated, is proposed and some practical implications are suggested.

References

1. Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (2012). *Neuropsychological assessment*. New York: Oxford U.P.
2. Eling, P. (2010). Onderwijs in de Neuropsychologie in een historisch en internationaal perspectief. In: Eling, P. (editor). *Geschiedenis van de neuropsychologie in Nederland.* Amsterdam: Uitgeverij Boom.
3. Simpson, D. (2005). Phrenology and the neurosciences: contributions of F.G. Gall and J.G. Spurzheim. *ANZ Journal of Surgery, 75* (6), 475-482.
4. Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bulletin de la Sociéte Anatomique, 6*, 330-357.
5. Berker, E.A., Berker, A.H., & Smith, A. (1986). Translation of Broca's 1865 Report: localisation of speech in the third left frontal convolution. *Archives of Neurology, 43* (10), 1065-1072.
6. Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. *Seminars in Neurology, 4* (2), 249-259.
7. Squire, L.R. (2009). The legacy of patient H.M. for neuroscience. *Neuron, 61* (1), 6-9.
8. Eling, P., & Kessels, R. (2012). Klinische neuropsychologie: een historische schets. In: Kessels, R., Eling, P., Ponds, R., Spikman, J., & van Zandvoort, M. (editors). *Klinische neuropsychologie.* Amsterdam: Uitgeverij Boom.
9. Wechsler, D. (1939). *The measurement of adult intelligence*. Baltimore: Williams & Wilkins.
10. Stroop, J. (1935). Studies of interference in serial verbal reaction. *Journal of Experimental Psychology, 18*, 643-662.
11. Rey, A. (1941). "L'examen psychologique dans les cas d'encephalopathie traumatique. (Les problems.)". *Archives de Psychologie,* 28, 215–285.
12. Wechsler, D. (1945). A standardized memory scale for clinical use. *The Journal of Psychology, 19* (1), 87-95.
13. Golden, C.J., Hammeke, T.A., & Purisch, A.D. (1980). *The Luria-Nebraska Neuropsychological Battery: Manual.* Los Angeles: Western Psychological Services.
14. Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests: administration, norms, and commentary*. New York: Oxford University Press.
15. Bouma, A., Mulder, J., Lindeboom, J., & Schmand, B. (2012). *Handboek Neuropsychologische Diagnostiek.* Amsterdam: Pearson Assessment and Information B.V.

CHAPTER 2

Ophthalmic impairment or higher-order visual deficit? Posterior cortical atrophy: a case report

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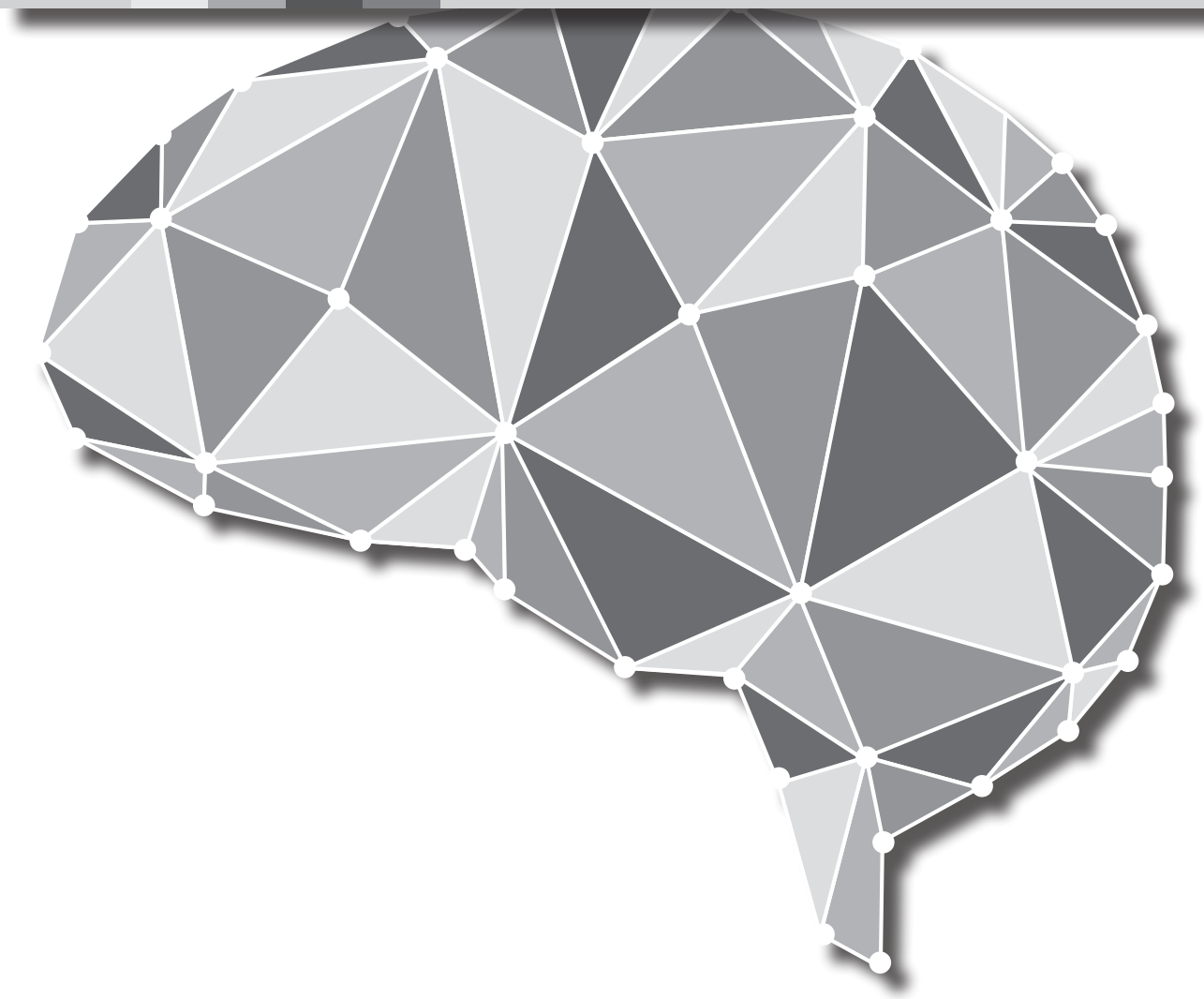
Applied Neuropsychology: Adult (2012), 19, 153-157



Abstract

A 64-year-old man (GK) was referred to our memory clinic because of progressive memory and concentration problems. His symptoms had started three years earlier with gradually increasing visual problems for which no ophthalmologic explanations could be found.

Neuropsychological assessment with detailed examination of the visuoperception revealed striking impairments in the higher-order visual functions, leading to a probable diagnosis of posterior cortical atrophy (PCA). The results of magnetic resonance imaging and cerebrospinal fluid examination supported the diagnosis.

PCA is considered the posterior variant of Alzheimer's disease that typically presents with problems in visuoperception or, less frequent, apraxia. Despite its clear clinical features, the diagnosis of PCA is often delayed because of the focus on ophthalmologic examination.

In this case report, the diagnosis of PCA in a 64-year-old man was not considered until further neuropsychological decay was evident. We argue that screening of higher-order visual functions can significantly contribute to an early diagnosis and treatment of PCA.

Introduction

Posterior cortical atrophy (PCA) was first described in 1988 (1) and is considered a variant of Alzheimer's disease (AD) in which the pathology is most prominent in the posterior parts of the brain. The neuropathology of PCA is similar to AD (2,3), although a more heterogeneous pathology is also reported (4). Magnetic resonance imaging (MRI) often reveals parieto-occipital atrophy and single photon emission computed tomography usually shows hypoperfusion in these regions (5). The clinical presentation of PCA differs from AD. Selective problems in visual perception, or in some cases apraxia, are characteristic presenting symptoms (6). In comparison to patients with AD, patients with PCA commonly complain about symptoms of visual dysfunction and problems in reading. Memory problems are less frequently reported (7,8). In a later stage of PCA a broad range of clinical features, such as Balint's syndrome and Gerstmann's syndrome can be present (9).

PCA is relatively unknown, and the problems in visual perception in these patients are often considered to be of ophthalmic origin instead of higher order visual deficits, causing delay in the diagnosis. This case report illustrates that assessment of the higher-order visual functions can be helpful. An early diagnosis is important because psychoeducation, medical treatment and other interventions are expected to be of greatest value in the early stages of dementia.

Case

GK is a 64-year-old former trader with a medical history of visual problems. He was diagnosed with amblyopia ('lazy eye') and esotropia of the left eye (eye turned inward). At the age of 55, his vision improved after surgery for esotropia. Six years later, GK visited his general practitioner again with new and progressive complaints of disturbed vision. In the following years, an optician, ophthalmologist and a specialized institute for impaired vision performed detailed examinations of the eyes but did not find a reasonable explanation for his new complaints. As GK also started reporting memory problems, he was referred to our memory clinic.

GK complained that he lost the lines while reading and he made errors in writing words. His handwriting became illegible. He had difficulties in estimating distances, for example, during driving or parking. Estimations of time durations were also difficult. Furthermore, he reported memory and concentration problems.

The neurological examination at the memory clinic was normal except for a left-sided hemianopia and slowness of verbal and motor responses. A brief neuropsychological screening revealed that GK's performances on multiple tests were impaired, and a possible dementia was considered.

Methods

To differentiate between different subtypes of dementia, an extensive neuropsychological assessment (NPA), MRI scan of the brain, and laboratory investigation of blood and cerebrospinal fluid (CSF) were performed, as well as a repeated ophthalmological assessment.

The NPA consisted of the Cambridge Cognitive Examination (CAMCOG; 10), Mini Mental State Examination (MMSE; 11), Boston Naming Test (12), token test (short form; 13), word fluency test (N and A, animals; 14), Wechsler Adult Intelligence Scale (WAIS-III; 15), Rey Auditory Verbal Learning Test (RAVLT; 16), Visual Association Test (VAT; 17), drawing a clock, house and spiral, ideational apraxia test (18), Stroop Color-Word Test (19), Trail-Making Test (TMT; 20) and the Behavioral Assessment of the Dysexecutive Syndrome (BADS; 21). The Cortical Visual Screening Test (CORVIST; 22) and the Visual Object and Space Perception Battery (VOSP; 23) were used to examine the problems in visuoperception in more detail. The CORVIST was designed to detect visual impairments in patients with normal vision in whom the visual symptoms cannot be explained by a routine ophthalmological, optometric or neurological examination (22). The CORVIST starts with a symbol acuity test to check for visual acuity. The subtests that follow measure higher-order visual functions such as face perception, size discrimination and reading of fragmented numbers. The VOSP was designed to detect deficits in object or space perception (23). A shape detection screening test is used to ensure that patients have adequate visual sensory capacities.

GK and his wife were informed about the ancillary tests described in this study, and GK signed an informed consent form for publishing the results.

Results

Laboratory investigations, including renal, liver, and thyroid function, vitamins B1 and B12, and a screening test for syphilis were all normal. The CSF showed a normal leukocyte count and a slightly increased protein level of 0.62 g/L (0.0-0.40). Tau and Ptau levels

were increased, whereas amyloid-ß (1-42) level was normal. Repeated ophthalmological assessment revealed a low vision of the left eye (3/300) corresponding to the pre-existing amblyopia, a vision of 0.7 of the right eye, and a left-sided hemianopia at perimetric testing. Extensive 7T-MRI investigation of the brain showed generalised atrophy, more pronounced in the right occipital region, without any ischemic or hemorrhagic abnormalities.

The results of the extensive NPA indicated an advanced stage of dementia. The MMSE was 21 out of 30. There were impairments in the domain of memory, executive functioning, and speed of information processing (Table 1). Language functions were unaffected and there were no signs of apraxia. More importantly, GK had striking impairments in the visuoperception and visuoconstruction.

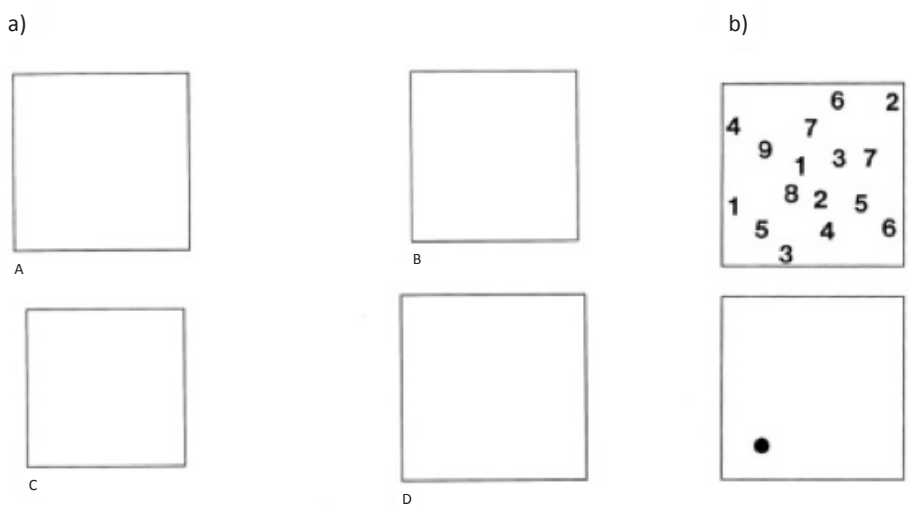
Results of the CORVIST showed adequate visual acuity (maximum score on screening test, corresponding to Snellen equivalent 6/9). When confronted with higher-order tasks, GK experienced profound difficulties. He was unable to discriminate the size of objects (Figure 1a) or to detect shapes of objects and hues. In addition, counting of scattered dots, reading of spatially crowded letters and numbers, and recognition of fragmented numbers were impaired. With regard to face perception, GK was unable to indicate the youngest or oldest person out of three pictures. The results on the VOSP were comparably affected. Again, GK had an optimal score on the screening test. However, he was not able to localize the position of a dot (Figure 1b; only the first subtest of the VOSP was administrated). Tests for visuoconstruction were also impaired (Figure 2).

Table 1 Test results of neuropsychological screening at the memory clinic and extensive neuropsychological assessment five months later.

Cognitive domain	Test	Neuropsychological screening	Neuropsychological assessment
Global cognitive functioning	CAMCOG		71/104**
	MMSE	24/30**	21/30**
Language	Boston Naming Test		77/87
	Token Test (short form)		15/21*
	Word Fluency		
	N (1 min)	15	15
	A (1 min)	13	13
	Animals (2 min)	23	16**
Working memory	Digit Span WAIS-III	10*	11
Long-term memory	RAVLT		
	Trial 1-5	3/4/5/4/4**	4/5/5/9/10
	Delay score	3*	4*
	Recognition score	20/30**	26/30**
	VAT		10/12*
Visuoperception	CORVIST		
	Symbol acuity		36/36
	Shape discrimination		8/8
	Size discrimination		0/2**
	Shape detection		0/8**
	Hue detection		2/4**
	Dot counting		2/4**
	Fragmented numbers		0/8**
	Face perception		7/8**
	Crowding test		2/4**
	VOSP		
	Screening test		20/20
	Number location		4/10**
Visuoconstruction	Clock	1/3**	1/3**
	House	Impaired	Impaired
	Spiral	Impaired	Impaired
	Interlocking Pentagons	Impaired	Impaired
Praxis	Ideational apraxia test		18/18
Attention	Stroop I	88 sec**	
	Stroop II	104 sec**	
	Stroop III	133 sec*(several lines were skipped!)	
Psychomotor speed	TMT A		GK was not able to perform this task
Executive functioning	BADS		
	Rule Shift Cards		Profilescore 0**
	Action Program		Profilescore 0**
	Key Search	Profilescore 3	Profilescore 4

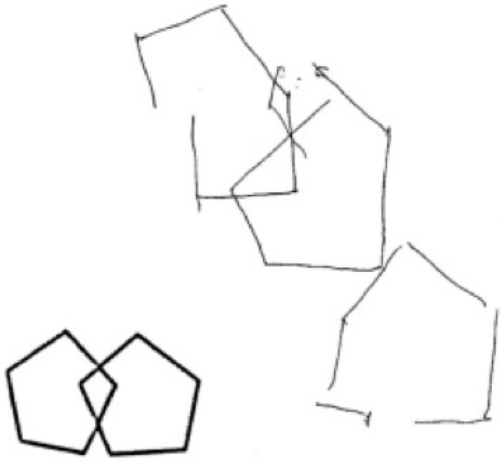
* below average performance (≤ 16e percentile); ** impaired performance (≤6e percentile).

Figure 1



a) Subtest *Size Discrimination Test* from *Cortical Vision Screening Test* (CORVIST). GK had to arrange the squares from big to small. The correct response is D A B C, GK's response is A B C D.
b) Subtest *Number Location* from the *Visual Object and Space Perception Battery* (VOSP). GK had to indentify the number corresponding with the position of the dot. He was only able to do this in a correct way in 4 out of 10 positions.

Figure 2 Copy of GK of interlocking pentagons from the Mini Mental State Examination.



The results of the NPA led to a probable diagnosis of PCA, and results of MRI and CSF examination supported this diagnosis. Subsequently, GK was prescribed galantamine, but he stopped taking it because of side effects. A year after the diagnosis GK was reporting more and more difficulties in daily life as a result of the higher-order visual problems. He experienced major problems in riding his bike, watching TV, and reading the newspaper, despite all kinds of vision aids.

Discussion

GK was diagnosed with PCA several years after the initial symptoms of a disturbed vision. He had a previous history of visual deficits, which improved after an operation and subsequently remained stable. Three years before presentation, he developed new and increasing visual complaints for which no ophthalmologic explanation was found. Only when he also began to suffer from progressive memory problems, clinical dementia was diagnosed. An extensive NPA with detailed examination of the higher-order cortical visual functions revealed a probable diagnosis of PCA, which was corroborated by MRI. The CSF markers showed abnormalities typically observed in AD and likewise in the PCA variant of this disease (24).

This case report shows that although patients can have a classical presentation of PCA, the diagnostic process can be delayed because of an exclusive focus on an ophthalmic cause. Most patients with PCA consult ophthalmological clinicians for their visual complaints (9), sometimes for a very long period. One patient described in an earlier study (25) was actually followed for 10 years by an ophthalmologist because of similar problems.

Because this is a single case report, the data should be interpreted with caution. Nevertheless, we think the diagnostic process of GK as described in this study is exemplary for many. Another limitation of this study is the absence of a follow-up NPA to confirm the progressive deterioration. Progression of both visual and memory problems of GK was based on the history from the patient and his wife in which a gradual progression of the symptoms was described.

More knowledge of PCA among clinicians can prevent delay in the diagnostic process. Patients who present with prominent problems in visual perception, such as problems in reading or difficulties in estimating distances, and in whom no ophthalmic explanation can be found, may suffer from PCA. Early neuropsychological assessment of higher-order visual perception aids the diagnosis.

Acknowledgements

We thank GK for his permission to describe and publish these findings. We would like to thank the authors and publisher of the CORVIST and the VOSP for their permission to use illustrations of these tests in this article.

References

1. Benson, D.F., Davis, R.J., & Snyder, B.D. (1988). Posterior Cortical Atrophy. *Archives of Neurology, 45*, 789-793.
2. Levine, D.N., Lee, J.M., & Fisher, C.M. (1993). The visual variant of Alzheimer's diasease: A clinicopathologic case study. *Neurology, 43*, 305-313.
3. Alladi, S., Xuereb, J., Bak, T., Nestor, P., Knibb, J., Patterson, K., & Hodges, J.R. (2007). Focal cortical presentation of Alzheimer's Disease. *Brain, 130*, 2636-2645.
4. Victoroff, J., Ross, W., Benson, F., Verity, A., & Vinters, H.V. (1994). Posterior Cortical Atrophy: Neuropathologic correlates. *Archives of Neurology, 51*, 269-274.
5. Whitwell, J.L., Jack, C.R., Kantarci, K., Weigand, S.D., Boeve, B.F., Knopman, D.S., Drubach, D.A., Tang-Waid, D.F., Petersen, R.C., & Joseph, K.A. (2007). Imaging correlates of posterior cortical atrophy. *Neurobiology of Aging, 28*, 1051-1061.
6. Aharon-Peretz, J., Israel, O., Goldsher, D., & Peretz, A. (1999). Posterior Cortical Atrophy Variants of Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 10*, 483-487.
7. Charles, R.F., & Hillis, A.E. (2005). Posterior cortical atrophy: Clinical presentation and cognitive deficits compared to Alzheimer's disease. *Behavioral Neurology, 16*, 15-23.
8. Migliaccio, R., Agosta, F., Rascovsky, K., Karydas, A., Bonasera, S., Rabinovici, G.D., Miller, B.L., & Gorno-Tempini, M.L. (2009). Clinical syndromes associated with posterior atrophy: Early age at onset AD spectrum. *Neurology, 73*, 1571–1578.
9. Mendez, M.F., Ghajarania, M., & Perryman, K.M. (2002). Posterior Cortical Atrophy: Clinical characteristics and differences compared to Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 14*, 33-40.
10. Roth, M., Tym, E., Mountjoy, C.Q., Huppert, F.A, Hendrie, H., & Goddard, R. (1988). *Camdex: The cambridge examination for mental disorders of the elderly*. Cambridge: Cambridge University Press.
11. Folstein, M.F., Folstein, S.E., & Mc Hugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.
12. Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia: Lea & Febiger.
13. Graetz, P., de Bleser, R., & Willmes, K. (1992). *Akense Afasie Test (Dutch)*. Lisse, the Netherlands: Swets & Zeitlinger.
14. Deelman, B.G., Koning-Haanstra, M., & Liebrand, W.B.G. (1981). *SAN Test: Een Afasie Test Voor Auditief en Mondeling Taalgebruik (Dutch).* Lisse, the Netherlands: Swets & Zeitlinger.
15. Wechsler, D. (1997). *Wechsler Adult Intelligence Scale (3rd ed)*. San Antonio, Texas: Psychological Corporation.
16. Rey, A. (1964). *L'Examen Clinique en Psychologie.* Paris: Presses Universitaires de France.
17. Lindeboom, J., Schmand, B., Tulner, L., Walstra, G., & Jonker, C. (2002). Visual association test to detect early dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery & Psychiatry, 73*, 126-133.
18. Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.
19. Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*, 643-662.
20. Corrigan, J.D., & Hinkeldey, N.S. (1987). Relationships between parts A and B of the Trail Making Test. *Journal of Clinical Psychology, 43*, 402-409.

21. Wilson, B.A., Alderman, N., Burgess, P.W., Emslie, H., & Evans, J.J. (2003).*Behavioural Assessment of the Dysexecutive Syndrome (BADS).* London: Thames Valley Test Company.
22. James, M., Plant, G.T., & Warrington, E.K. (2001). *CORVIST: Cortical Vision Screening Test*. Bury St Edmunds: Thames Valley Test Company Limited.
23. Warrington, E.K., & James, M. (1991). *The Visual Object and Space Perception Battery*. Bury St Edmunds: Thames Valley Test Company.
24. Baumann, T.P., Duyar, H., Sollberger, M., Kuhle, J., Regeniter, A., Gomez-Mancilla, B., Schmidtke, K., & Monsch, A.U. (2010). CSF-Tau and CSF-Aβ_{1-42} in Posterior Cortical Atrophy. *Dementia and Geriatric Cognitive Disorders, 29*, 530-533.
25. Karner, E., Jenner, C., Donnemiller, E., Delazer, M., & Benke, T. (2006). The clinical syndrome of posterior cortical atrophy [article in German]. *Nervenartz, 77*, 208-214.

CHAPTER 3

Cognitive disorders after sporadic ecstasy use? A case report

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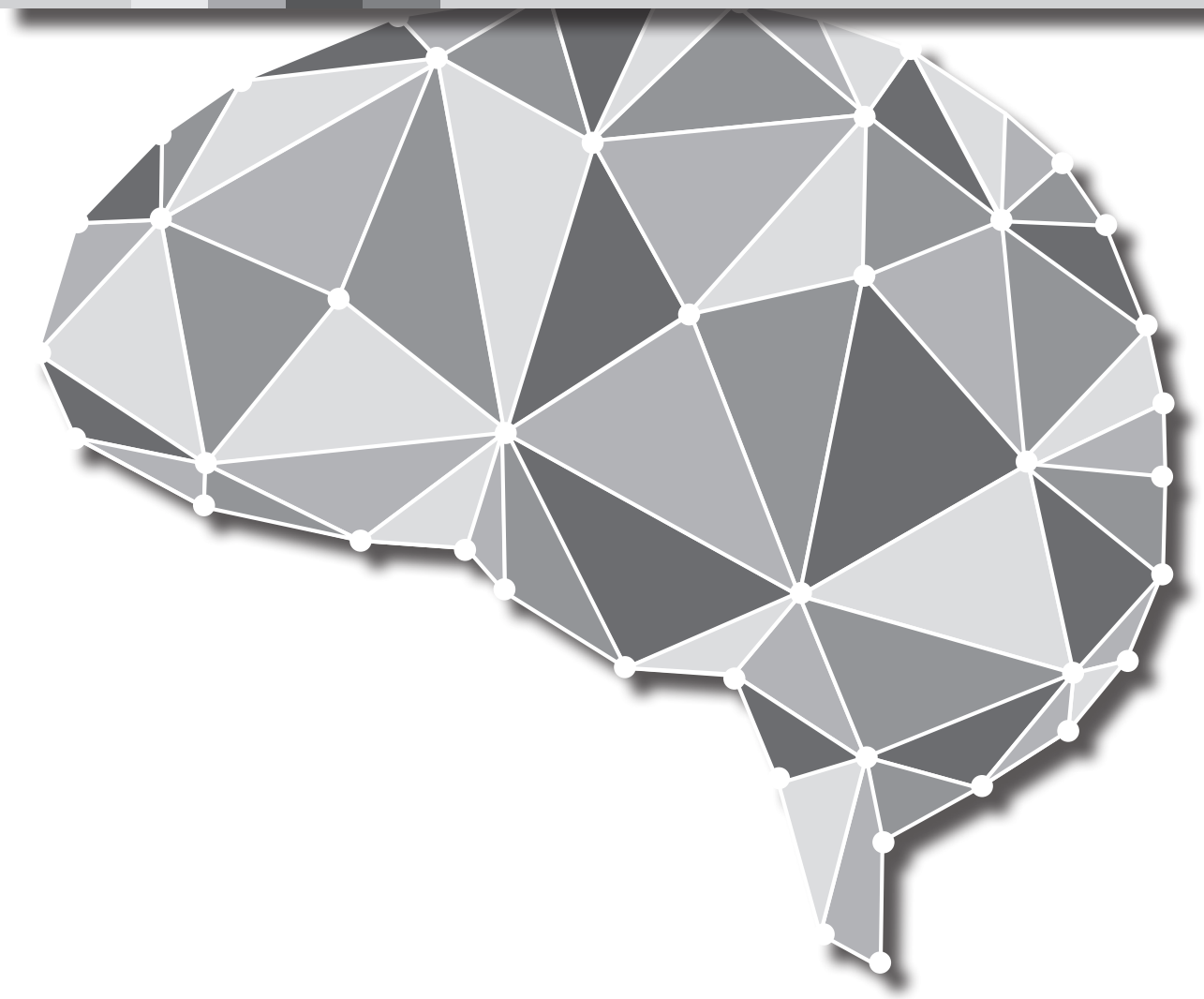
Neurocase (2014), DOI: 10.1080/23306343.2014.886398



Abstract

Memory problems and changes in hippocampal structures after chronic ecstasy use are well described in the literature. Cognitive problems after incidental ecstasy use are rare, and the few patients described in case reports returned to their normal cognitive level after a relative short period.

FV is a 39-year old man who used an ecstasy tablet in 2005. This resulted in severe confusion for a few days. The confusion was followed by persistent memory complaints and difficulties orientating in new surroundings. An extensive neuropsychological examination seven years after the ecstasy use revealed a severe memory disorder. Furthermore, his performance on a virtual reality test of navigation showed serious problems navigating in new surroundings. In comparison with matched control subjects (Bayesian approach for single case studies) his scores were significantly impaired on several subtasks of the navigation test.

On a MRI-scan of the brain bilateral hippocampal atrophy and sclerosis were visible, comparable to previous MRI studies describing hippocampal damage following ecstasy ingestion.

This case report describes persistent memory and navigation disorders after sporadic ecstasy use, supported by structural brain abnormalities seen on the MRI-scan. These findings revive the debate on whether sporadic ecstasy use can cause persistent cognitive deficits.

Introduction

Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA) is frequently associated with changes in cognitive functioning. The effect of chronic use of this drug on cognition has been studied intensively and most studies reported a negative effect of ecstasy on cognitive functioning. For example, McCardle et al. (1) investigated the effect of the drug on cognition and mood and concluded that chronic users had memory and attention problems. Furthermore, they had higher scores on depression scales in comparison to a control group. Cognitive impairments as a result of ecstasy use are also described in a review study of Parrott (2) and a more recent review study of Chummun, Tilley & Ibe (3).

The cognitive impairments following ecstasy use seem to be the result of changes in serotonin and dopamine levels (3). Cognitive deficits as memory problems may reflect the serotonergic changes in the hippocampus (2), although not all studies report hippocampal changes (4). The serotonin syndrome described by Parrot (5) includes physical changes (e.g. behavioural hyperactivity, hyperreflexia, tremor) but also mental confusion. Chronic methamphetamine use is also related to severe gray-matter deficits in cingulate, limbic and paralimbic cortices (6).

As explained before, most studies involving ecstasy have focussed on the chronic use of this drug. The effect of recreational doses or low doses of ecstasy is less studied, and in most of the studies on low doses no clear relation between this drug and cognitive deficits has been found. A double-blind placebo-controlled study of Vollenweider et al. (7) investigated the relation between a recreational dose of ecstasy and the acute effects on psychological and cardiovascular measures in participants without any history of drug use. The Stroop Color-Word Test measured attention and there were no differences found in performances of participants using ecstasy and participants using a placebo. In contrast, Gouzoulis-Mayfrank et al. (8) reveal a worse performance of recreational ecstasy users on multiple cognitive tests in comparison to a control group. Although the authors of this study describe the use of ecstasy in their participants as ‘recreational’, subjects used ecstasy 6 months or longer with a minimum frequency of twice a month or at least 25 occasions during the past 2 years. Jager et al. (9) investigated the effect of incidental use of ecstasy on cognition. Participants in this study had used 2 tablets on average and were tested before and after the ecstasy use. No significant effects of these low doses of ecstasy on cognitive functioning were found. Another study (10) analysed the acute effects of 100 mg of MDMA on cognitive functioning. Negative effects on attention and working memory tests were founded, but differences in performances were mostly diminished after 24 hours. Participants in this study all had a history of drug use, which makes a comparison with the study of Jager et al. difficult.

The effects of incidental ecstasy use on brain structures have also been studied. De Win et al. (11) analysed the effects of low doses of ecstasy on the brain by comparing different brain areas with multiple imaging techniques. They did not find indications for structural neuronal damage in subjects who used ecstasy for the first time (11).

Taken together, the chronic use of ecstasy seems to have a negative effect on cognition, and hippocampal changes have been related to the chronic usage of this drug. Studies analysing the effects of low doses of ecstasy on cognition and brain structures mostly did not find such effects.

In this case report we describe a 39-year-old man, who reported severe memory and navigation problems after incidental ecstasy use. We examined the cognitive status of this patient seven years after the ingestion. Standard neuropsychological tests were used to measure memory capacities. To analyse patients' navigation problems we made use of a more experimental virtual reality test. This case reopens the discussion whether a low dose of ecstasy can cause severe and persistent cognitive disorders.

Methods

Case

FV is a 39-year-old, highly educated man. In 2005 FV had used one ecstasy tablet on a party, and directly afterwards he was confused, had trouble speaking correctly and he reported memory problems. After a day, the confusion and language problems disappeared, but the memory problems still remained. Two months after the ecstasy use FV visited the neurological outpatient clinic of the University Medical Center Utrecht. The neurological exam was normal and because the memory problems were in remission and further improvement was expected no imaging techniques were performed. In the years following this incident the memory problems reduced somewhat, but FV never came back to his old level of functioning. Therefore, in 2012, he visited the neurological outpatient clinic again. At that time FV reported problems in remembering appointments and information people told him. FV also reported difficulties orientating in new surroundings. He frequently made use of navigation equipment, both in his car and when biking (application on his smart phone). Just studying route information before leaving home was not sufficient. When parking his car he had to write down the location of this place, otherwise, he was not able to find his car back.

Medical history

FV reported he used ecstasy 5 to 6 times in the period 2002-2005. He states never to have used drugs after 2005. Friends of FV confirm that he was a sporadic user of ecstasy. He suffered from hypertension but besides that there was no relevant medical history. He did not suffer from epilepsy. FV did not use any medication. Before 2005 FV had no cognitive complaints. He graduated from university, worked several years at an academic level and started his own business, just before the ecstasy ingestion.

Neuropsychological assessment

To measure FV's cognitive status an extensive neuropsychological assessment was administrated. The most important cognitive domains (intelligence, language, visuoperception- and construction, attention and executive functions, psychomotor speed) were measured and besides that a test for malingering and a depression scale were added to the assessment. In particular the memory domain was measured in detail, and tests focussing on different memory processes were administrated. Working memory was assessed by the Digit Span of the Wechsler Adult Intelligence Scale – third edition (WAIS-III) (12) and the Corsi Block Tapping test (13), verbal (long term) memory by the Rey Auditory Verbal Learning Test (RAVLT) (14) and story recall of the Rivermead Behavioral Memory Test (RBMT) (15), and visual (long term) memory by the Location Learning Test (LLT) (16), Benton Visual Retention Test (BVRT) (17) and the Modified Taylor Complex Figure (18). To examine anterograde amnesia the Visual Association Test (VAT) (19) was used and nonverbal recognition skills were assessed by the Doors Test (20) and the Continuous Visual Memory Test (CVMT) (21).

Navigation experiment

Besides general memory problems, FV also complained about problems navigation in new surroundings. Because a standardized neuropsychological assessment does not include tests to measure navigation skills properly, we added a virtual reality test of navigation to our assessment. This test, making use of the virtual Tübingen environment, was designed to measure navigation skills in a more complex and therefore realistic manner (see e.g. 22). In this test, subjects are shown and asked to memorize a video of a route in virtual Tübingen. Afterwards different subtasks are administered; scene recognition, route continuation, route sequence, route order, route position, route distance, pointing, route drawing and map recognition. *Scene recognition* concerns the recognition of 11 scenes shown in the movie, among 11 distractor scenes. *Route continuation* entails the indication of what turn was taken at 11 intersections. In the *route sequence task*, participants are asked to indicate the turns taken during the route by aligning arrows on small paper cards, accordingly. In the *route order task*, participants arrange 11 scenes in the order they appeared on the route.

The route position, route distance, and pointing subtasks concern the geometrical features of the route. In *route position*, participants are asked to indicate the position of each of 11 scenes by drawing a vertical line on a horizontal line representing the total distance of the route. In the *route distance* subtask, they have to indicate the relative distance between two points on the route on a horizontal line, also representing the total distance of the route. In the *pointing task*, participants indicated the direction of their starting point and endpoint at each of the 11 scenes. A manual rotation device was used, on which the experimenter could read the responses in degrees. Finally, knowledge of the route layout was tested by means of *route drawing* and map recognition. First, the participant was asked to draw the route onto a map of the environment, in which only the starting point and starting direction was indicated. In the *map recognition* subtask, the participant was shown four possible maps of the route, and asked to point out the correct map.

Control Subjects

To compare FV's performance of the task in the virtual environment, four matched control subjects were recruited. Mean age of the control subjects was 38.0 years (SD 3.7, range 34-42), all of them were similar to FV high educated (higher professional education or academic degree). The control subjects had no history of drug use.

Brain imaging

A routine clinical Magnetic Resonance Imaging (MRI) scan was performed on a 1,5 Tesla scanner (Philips Medical Systems, Best, The Netherlands). The protocol included a transversal T2-weighted turbospin-echo (repetition time [TR]/echo time [TE]/inversion time 2200/10 and 2200/100ms), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time [TI] 6158/100/2000 ms), and diffusion weighted imaging (DWI) (TR/TE 2258/81, b value 0/1000) sequences (slice thickness 6 mm, slice gap1.2mm, 19 slices), and a coronal T1-weighted Inversion Recovery (IR) (TR/TE/TI 2892/22/410 ms) (slice thickness 4 mm, 38 contiguous slices).

Laboratory investigation

Laboratory investigations included a full blood count, serum creatine and electrolytes, liver function tests, thiamine, vitamin B12 and thyroid function. Furthermore, serologic testing for Lues and HIV was performed.

Statistical methods

FV's performances on the neuropsychological assessment were compared with normative data corrected for sex, age and education level. Scores below the 16th percentile are called *below average*, scores below the 6th percentile are called *impaired*.

To compare FV with the matched control subjects we made use of the Bayesian approach for single case studies (23).

Results

Neuropsychological assessment

The neuropsychological assessment revealed no cognitive disorders in the language, visuoperception and -construction, attention and executive domain. All scores were average or above average (in comparison to normative data, corrected for sex, age and education level). Psychomotor speed was above average. The premorbid verbal intelligence level was average; nonverbal intelligence level is high average. There were no signs of a depressed mood. The score on a malinger test was optimal.

FV's performances on memory tests were striking. Working memory was on average level, but scores on all memory tests for long term memory were below average or impaired. There were no differences in performances on verbal or nonverbal tests, except the more average scores on visual recognition tasks (Doors Test, CVMT). See table 1 for a detailed description of FV's performance on the memory tests.

Table 1 FV's performances on memory tasks of the neuropsychological assessment, compared with normative data corrected for sex, age and education level.

Cognitive domain	Test	FV's score
Working Memory	Digit span	15/30
	Corsi Block Tapping	16/30
Long term memory	RAVLT	
	Immediate recall	7/8/8/8/7 **
	Delayed recall	2/15 **
	Recognition	25/30 **
	LLT	
	Immediate recall (displacements)	22/15/13/16/9 **
	Delayed recall	19 **
	RBMT stories	
	Immediate recall	8 **
	Delayed recall	0,5 **
	Doors Test	17/24 *
	Modified Taylor Complex Figure (delayed recall)	2,5 **
	VAT	8/12 **
	CVMT	80
	BVRT	Correct: 6 *
		Error: 4 *

* Below average performance (≤16^{e} percentile), ** Impaired performance (≤6^{e} percentile).

Navigation experiment

FV's performance on the subtests *route continuation*, *route sequence* and *route distance* were significantly worse in comparison to matched control subjects (two-tailed tested, *p*=.04 to .05). His performance on the subtest *route position* was significantly worse on a one-tailed test (*p*=.04), and almost significant on a two-tailed test (*p*=.08). Furthermore, while all the control subjects were able to recognize the right map out of four, FV selected one of the incorrect alternatives (see table 2). FV's performance on the subtests *route recognition*, *route order*, *pointing* and *map drawing* was not significant different from the control subjects.

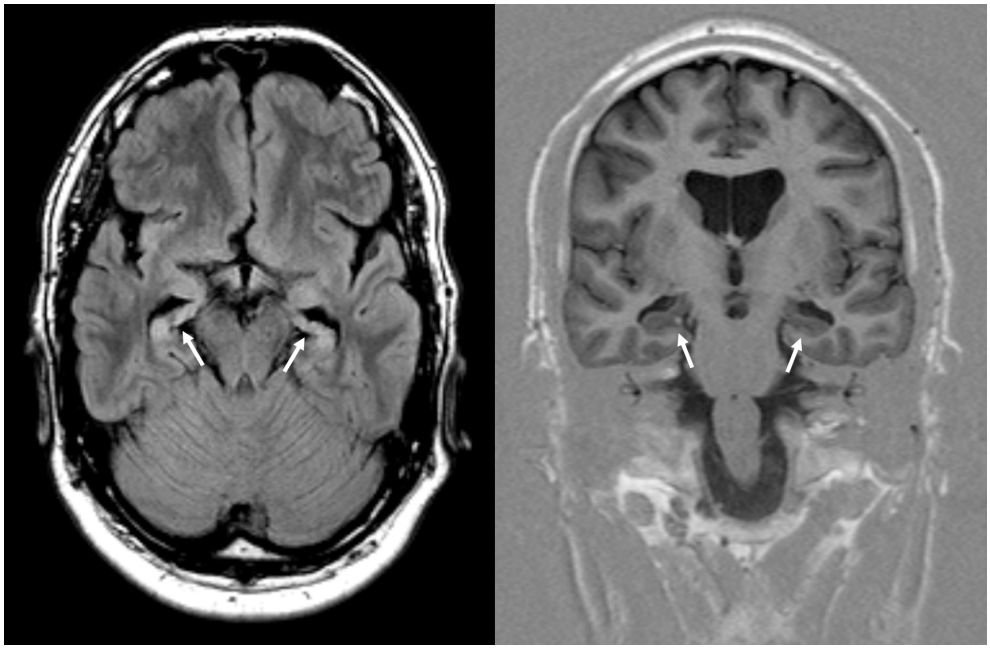
Table 2 FV's performance on the navigation experiment.

Subtest	FV's score	Mean score and SD of control subjects	*t* and *p*
Scene recognition (% correct)	86	88 (16)	-.112 (n.s.)
Route continuation (% correct)	45	91 (13)	-3.17 (.05)
Route sequence (items correct)	0	5.75 (1.5)	-3.43 (.04)
Route order (score 0-22)	3	14.5 (7.1)	-1.45 (n.s.)
Route position (degrees deviation)	30	14 (5.4)	2.65 (.08)
Route distance (degrees deviation)	35	9.3 (7.4)	3.11 (.04)
Pointing starting point (degrees deviation)	73	51 (16)	1.23 (n.s.)
Pointing endpoint (degrees deviation)	79	61.8 (11)	1.40 (n.s.)
Map drawing (cm correct)	31	69.8 (34)	-1.02 (n.s.)
Map recognition	incorrect	correct	

MRI

On brain MRI bilateral hippocampal atrophy was observed on coronal T1 weighted images, corresponding with Medial Temporal lobe Atrophy (MTA) score 2. FLAIR and T2 weighted TSE sequences showed increased signal of both hippocampi, without increased signal on DWI, which could indicate sclerosis (see figure 1). Besides signs of hippocampal atrophy and sclerosis, the MRI scan was normal, and no other abnormalities (e.g. vascular lesions, tumors) were seen that could explain the cognitive impairments.

Figure 1 Bilateral atrophy and sclerosis of the hippocampi.



Left: Fluid attenuation inversion recovery (FLAIR) sequence, showing increased signal of both hippocampi (arrows), which could indicate sclerosis.
Right: T1-weighted inversion recovery (IR) coronal image, showing volume loss of the hippocampi on both sides (arrows), Medial Temporal lobe Atrophy (MTA) score 2.

Laboratory investigation

Laboratory investigations were all normal, even as serologic testing for Lues and HIV.

Discussion

FV is a 39-year-old man who suffers from serious memory and navigation problems after sporadic ecstasy use. FV has great difficulties in daily life remembering appointments or things people told him. Furthermore, he is not able to navigate appropriate in new surroundings and gets lost when he is not using navigation tools.

In line with the complaints FV reported, the neuropsychological assessment revealed major memory disorders. On the virtual reality test of navigation FV had significantly worse scores on different subtests in comparison to matched control subjects. He had trouble remembering what turns were made on the route and he had no 'internal map' of the route. He also had difficulties remembering the geometrical features of the route (position

of scenes on the route and relative distance between to scenes on the route). Finally, he was unable to select the correct map out of four potential maps. Strikingly, he was able to recognize scenes from the route, remembered their order, and the direction of the start and end of the route. Therefore, his impairment in navigation skills cannot simply be explained by a general memorization problem, as not all navigation aspects tested were impaired. The findings of the neuropsychological assessment and the virtual reality test can explain the complaints of FV in daily life fully. Importantly, the cognitive problems appear to have arisen directly after the ecstasy ingestion in 2005 and therefore we related the cognitive problems to the use of this drug. The relation with ecstasy use is further supported by the structural changes in the hippocampus seen on the MRI scan of FV. The hippocampus plays a crucial role in memory processes (24) but also in the ability to navigate (25, 26).

To our knowledge, this is the first demonstration of persistent cognitive disorders after sporadic use of ecstasy. Gardner et al. (27) also described two cases with acute hippocampal changes on MRI after ecstasy ingestion. These patients reported cognitive problems, but those diminished after a relatively short period. The first patient used half a tablet ecstasy every few months (not further specified). After ecstasy ingestion he had tonic-clonic seizures and on the MRI scan of the brain two days later high signal and swelling of the hippocampus was seen. A later scan showed hippocampal atrophy. After a few months this patient was asymptomatic and had returned to work. The second case had also seizures after ecstasy use, followed by confusion and memory difficulties. She returned to work within a few days and the cognitive complaints disappeared in the following months. On her MRI scan a similar swelling of the hippocampus followed by atrophy was seen, as is also described in our patient.

This case report reopens the discussion whether sporadic ecstasy use is harmful or not. In previous years the risks of a recreational dose of ecstasy was discussed. In the study of Vollenweider et al. (7) subjects received a dose of MDMA. Gijsman et al. (28) discussed the administration of this dose to healthy subjects. They stated that, based on animal research, it cannot be excluded that the rapid decrease in concentration of serotonin after a single dose of ecstasy does not cause damage of the serotonergic neurons. Vollenweider and colleagues (29) responded to these statements by explaining that reductions in serotonin levels do not automatically results in serotonergic neurodegeneration (30,31). A more recent study of Jager et al. (9) did not find evidence for effects of a low dose of ecstasy on cognitive functioning.

In light of the currently available evidence it is still not totally clear what the precise consequences are of a low dose of ecstasy. Our case report describes, in contrast to the

other studies, persistent and severe cognitive deficits after sporadic ecstasy use. A few aspects of this study may raise questions and need to be discussed.

Although FV stated that before 2005 he did not have any cognitive complaints, we have no previous neuropsychological assessment to compare the current test scores to. We cannot fully establish that there were no cognitive deficits before the ecstasy use. Nonetheless, FV obtained a Master's degree without any problems and there were no signs of any cognitive problems in daily or professional life.

Another issue of discussion involves the etiology of the cognitive disorders. Based on the story of FV we assume that the problems arose directly afterwards the ecstasy ingestion. The kind of cognitive disorders, even as the kind of hippocampal damage, have been associated to (chronic) ecstasy use in previous studies. Taken these facts together, we assume that the cognitive disorders and the hippocampal changes of FV are the result of his ecstasy use in 2005. This assumption is strengthened by the fact that the MRI scan did not reveal vascular lesions, tumors or other causes that could explain the cognitive impairments. Laboratory investigations were also normal and gave no indications for alternative explanations. We did not find any indications for a depressed mood or for malingering. Finally, FV was not involved in litigation. Nevertheless, we cannot fully exclude all other possible causes (for example hypoxia during an epileptic attack) and it is regrettable that no imaging techniques were performed directly after the ecstasy ingestion.

One could doubt whether the ecstasy FV had taken was pure MDMA or also contained other substances. Directly after the incident the other pills FV and his friends had bought were tested by the Trimbos Instituut (centre of expertise on mental health and addiction). Test results showed that the pills contained 150 mg pure MDMA.

As mentioned in the introduction cognitive disorders after chronic ecstasy use are frequently described in the literature. FV states that he only used ecstasy sporadically in the period 2002-2005. His friends confirm this low use of ecstasy. The marked alteration in functioning of FV is striking, and is not expected after chronic use.

Because this is a single case report we should be cautious in drawing conclusions. Nevertheless, the present findings may help further understanding of the relation between ecstasy use and cognition. Taken together, this case report describes a man with severe and persistent cognitive disorders after incidental ecstasy use. On his MRI scan of the brain hippocampal atrophy was seen. These findings call for closer examination of individual cases on the effects of low doses of ecstasy on cognition and on brain structures. Is it possible that

more cases such as these exist but that individual stories are neglected by studying large groups?

Acknowledgements

We would like to thank FV for his cooperation during the assessments and his permission to publish this data. We are also very grateful to the control subjects who participated in this study. Finally, we thank Geert Jan Biessels for his critical reading of this manuscript.

References

1. McCardle, K., Luebbers, S., Carter, J.D., Croft, R.J. & Stough, C. (2004): Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology, 173*, 434-439.
2. Parrott, A.C. (2001). Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology: Clinical and Experimental, 16* (8), 557-577.
3. Chummun, H., Tilley, V., Ibe, J. (2010). 3,4-methylenedioxyamfetamine (ecstasy) use reduces cognition. *British Journal of Nursing, 19* (2), 94-100.
4. Obergriesser, T., Ende, G., Braus, D.F. & Henn, F.A. (2001). Hippocampal 1H-MRSI in ecstasy users. *European Archives of Psychiatry and Clinical Neuroscience, 251*, 114-116.
5. Parrott, A.C. (2002). Recreational ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology, Biochemistry and Behavior, 71*, 837-844.
6. Thompson, P.M., Hayashi, K.M., Simon, S.L., Geage, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W. & London, E.D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *The Journal of Neuroscience, 24* (26), 6028-6036.
7. Vollenweider, F., Gamma, A., Liechti, M. & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology, 19* (4), 241-251.
8. Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H.J., Fimm, B. & Sass, H. (2000). Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *Journal of Neurology, Neurosurgery & Psychiatry, 68*, 719-725.
9. Jager, G., de Win, M.M., Vervaeke, H.K., Schilt, T., Kahn, R.S., van den Brink, W., van Ree, J.M. & Ramsey, N.F. (2007). Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study. *Psychopharmacology, 193*, 403-414.
10. Stough, C., King, R., Papafotiou, K., Swann, P., Ogden, E., Wesnes, K. & Downey, L.A. (2012). The acute effects of 3,4- methylenedioxyamfetamine and d-methamphetamine on human cognitive functioning. *Psychopharmacology, 220*, 799-807.
11. De Win, M.M.L., Reneman, L., Jager, G., Vlieger, E.J.P., Olabarriaga, S.D., Lavini, C., Bisschops, I., Mojoie, C.B.L.M., Booij, J., den Heeten, G.J. & van den Brink, W. (2007). A prospective cohort study on stustained effects of low-dose ecstasy on the brain in new ecstasy users. *Neuropsychopharmacology, 32*, 458-470.
12. Wechsler, D. (1997). *Wechsler Adult Intelligence Scale, 3rd ed*. San Antonio, Texas: Psychological Corporation.
13. Kessels, R.P.C., Van Zandvoort, M.J.E., Postma, A., Kappelle, L.J. & De Haan, E.H.F. (2000). The Corsi Block-Tapping Task: Standardization and Normative Data. *Applied Neuropsychology: Adult, 7* (4), 252-258.
14. Van der Elst, W., Van Boxtel, M.P., Van Breukelen, G.J. & Jolles (2005). J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society, 11*, 290-302.
15. Van Balen, H.G.G. & Wimmers, M.F.H.G. (1993). *Rivermead Behavioural Memory Test: Normeringsgegevens voor Nederland en Vlaanderen.* Lisse: Swets en Zeitlinger B.V.
16. Kessels, R.P.C., Bucks, R.S., Willison, J.R. & Byrne, L.M.T. (2012). *Location Learning Test, Herziene uitgave: Handleiding.* Amsterdam: Hogrefe Uitgevers B.V.
17. Sivan, A.B. (1992). *Benton Visual Retention Test Fifth Edition: Manual*. San Antonio, TX: The Psychological Corporation.

18. Hubley, A.M. & Tremblay, D. (2002). Comparability of total score performance on the Rey-Osterrieth Complex Figure and a modified Taylor Complex Figure. *Journal of Clinical and Experimental Neuropsychology, 24*, 370-382.
19. Lindeboom, J., Schmand, B., Tulner, L., Walstra, G. & Jonker, C. (2002). Visual Association Test to detect early dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery and Psychiatry, 73*, 126-133.
20. Baddeley, A., Emslie, H. & Nimmo-Smith, I. (1994). *Doors and People: Manual*. Bury St Edmunds: Thames Valley Test Compagny.
21. Trahan, D.E. & Larrabee, G.L. (1988). *Continuous Visual Memory Test: Profession Manual*. Odessa, FL: Psychological Assessment Resources, Inc.
22. Van der Ham, C.J.M., Van Zandvoort, M.J.E., Meilinger, T., Bosch, S.E., Kant, N. & Postma, A. (2010). Spatial and temporal aspects of navigation in two neurological patients. *NeuroReport, 21* (10), 685-689.
23. Crawford, J.R. & Garthwaite, P.H. (2007). Comparison of a single case to a control or normative sample in neuropsychology: Development of a Bayesian approach. *Cognitive Neuropsychology, 24* (4), 343-372.
24. Eichenbaum, H. (2004). Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron, 44*, 109-120.
25. Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S.J., Frith, C.D. & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science, 280*, 921-924.
26. Goodrich-Hunsaker, N.J., Livingstone, S.A., Skelton, R.W. & Hopkins, R.O. (2010). Spatial deficits in a virtual water maze in amnesic participants with hippocampal damage. *Hippocampus, 240*, 481-491.
27. Gardner, H., Lawn, N., Fatovich, D.M. & Archner, J.S. (2009). Acute Hippocampal Sclerosis Following Exctasy Ingestion. *Neurology, 73*, 567-569.
28. Gijsman, H.J., Verkes, R.J., van Gerven, J.M.A. & Cohen, A.F. (1999). MDMA study. *Neuropsychopharmacology, 21*, 597.
29. Vollenweider, F.X., Gamma, A., Liechti, M. & Huber, T. (1999). Is a single dose of MDMA harmless? *Neuropsychopharmacology, 21*, 598-600.
30. Colado, M.I., Williams, J.L., & Green, A.R. (1995). The hyperthermic and neurotoxix effects of "Ecstasy" and 3,4, methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. *British Journal of Pharmacology, 115*, 1281-1289.
31. Oshea, E., Granados, R., Esteban, B., Colado, M.I. & Green, A.R. (1998). The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA (Ecstasy). *Neuropharmacology, 37*, 919-926.

CHAPTER 4

Symptom Checklist 90-Revised in neurological outpatients

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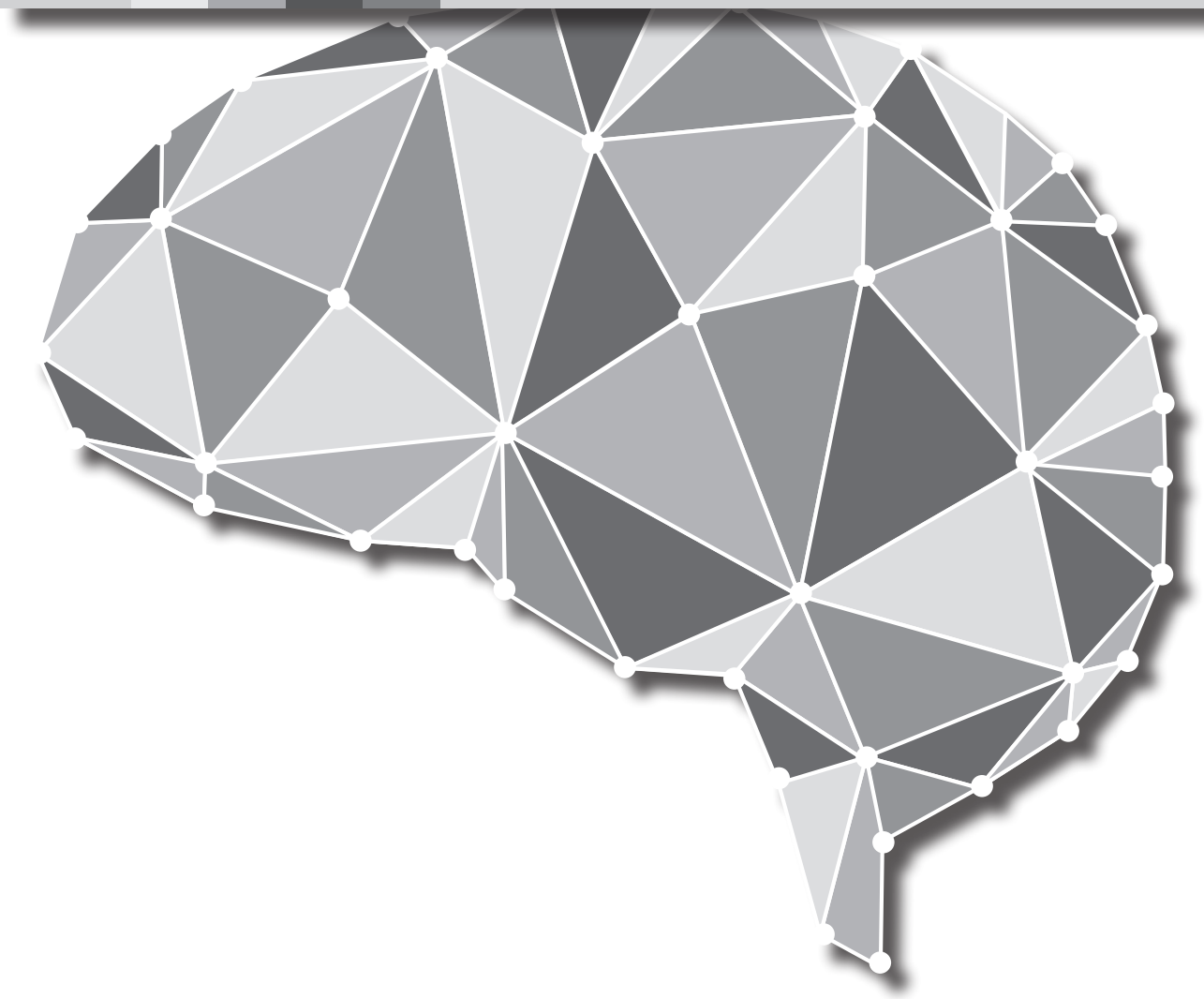
Journal of Clinical and Experimental Neuropsychology (2014),
DOI: 10.1080/13803395.2013.875519



Abstract

The SCL-90-R is an international, widely used self-report questionnaire of multidimensional complaints with normative data for healthy control subjects and psychiatric patients. The questionnaire is also often used in neurological patients. Little is known about the amount and pattern of complaints in this group and normative data are lacking. We therefore analysed self-reported symptoms on the SCL-90-R of a neurological population (*N*=600). Moreover, we compared the answer patterns of five subgroups: neurodegenerative disease, cerebrovascular disease, epilepsy, brain tumor, and traumatic brain injury.

Neurological outpatients scored significantly higher in comparison with normative data from healthy control subjects, with most pronounced scores on *Inadequacy of Thinking and Acting*, *Depression*, and *Somatization* (p<.01, effect sizes 1.69, .83, and .83). No differences between the various pathologies were found.

Although it is difficult to determine whether the complaints arise directly from the neurological disease or more indirectly from psychiatric disturbances accompanying the disease, simply comparing a neurological patient to normative data for healthy control subjects can lead to inappropriate classifications. Complaints of our patients should not be directly interpreted as psychopathology. A two-step procedure in which scores on the SCL-90-R are first compared to healthy control subjects and secondly to neurological patients can be helpful in the interpretation.

Introduction

The Symptom Checklist-90 (1) is an international self-report questionnaire of multidimensional complaints and is widely used by clinical health psychologists (2). The questionnaire was designed in the early seventies to measure psychopathology (described in manual as psychiatric and psychosomatic symptoms) and has been translated into many languages since then.

The revised version of the SCL-90 (3,4) has 90 items loading on 9 subscales reflecting multiple dimensions of psychological and somatic complaints and gives a general measurement of psychopathology. Item selection is based on self-reports of patients and is complemented with a-priori classifications of clinicians. The questionnaire as used in the United States has four normative data groups: adult healthy control subjects, adolescent healthy control subjects, adult psychiatric outpatients and adult psychiatric inpatients.

In clinical neuropsychology the SCL-90-R is often used as part of neuropsychological assessment to examine the amount of psychiatric or physical complaints (e.g. 5,6). The assessment of emotions and personality is an important part of the neuropsychological examination, because these factors may affect a patient's ability to perform at their optimal capacity which can result in cognitive impairments (7). On the other hand, those factors can also be contributory to the diagnostic process, for example in differentiating between depression and the early stage of a neurodegenerative disorder (5). An important shortcoming in the administration of questionnaires in general in a neurological population is the absence of specific normative data. The applicability of personality questionnaires in neurological patients has been subject of discussion in different studies and multiple limitations have been described (e.g. 8-11). Many limitations also hold for the administration of the SCL-90-R in this population. Although previous studies about the use of the SCL-90-R in neurological patients are sparse, they suggest that this usage could lead to inappropriate classifications, as in the study of Kaplan et al. (12) who described the interpretive risk of the SCL-90-R in patients with brain tumors. These patients reported high levels of somatic and obsessive-compulsive complaints as well as psychotic disorders. Traditional interpretation of these data may result in inappropriate classifications or psychiatric overinterpretation, because patients endorse certain items related to physical illnesses (5). For example, one of the patients described by Kaplan reported hallucinations. The symptoms of this patient were not the result of a psychotic disorder or psychological symptoms, but were due to the tumor (12). The authors suggest that appropriate normative data would improve the interpretation of the scores.

In another study Kaplan (13) analysed the feasibility of a correction factor for the SCL-90-R in this patient group, based on previous work of Gass and Wald (14) who presented a similar correction factor for the Minnesota Multiphasic Personality Inventory (MMPI) in patients with neurological diseases. At first, the correction factor appeared to improve the utility of this questionnaire in patients with brain tumors, but further analyses revealed an unacceptably low sensitivity and poor ecological validity (13). Kaplan concluded that interpretation of this questionnaire in patients with brain lesions should be done with high caution and multimodal assessments should be administrated to improve the measurement of psychopathology.

Limitations in the use of the SCL-90-R have also been described for other specific neurological patient groups, e.g. patients with spinal cord injuries (15), mild to moderate brain injury (16,17), head trauma (18) and stroke (19). These studies indicate limited validity of the SCL-90-R in a neurological patient group with respect to psychopathology.

Taken together, limitations in the usage of the SCL-90-R in neurological patients have been described in several studies. Results show that neurological patients have elevated scores on the SCL-90-R, and the underlying neurological disease seems to contribute to this high score. A correction factor after item-analyses seems not helpful. Almost all authors suggest that interpretation of the SCL-90-R scores should be done with high caution and special normative data may be contributory. Important shortcomings of previous studies were the small group sizes and the very specific neurological diseases that were analysed, limiting the generalizability of the results.

The aims of this study was to deepen the previous discussion in the literature by analysing the possible elevated level of complaints in a large group of neurological outpatients and discuss the usage of normative data from healthy control subjects. Therefore we analysed scoring patterns of the SCL-90-R in a noteworthy sample of neurological outpatients and studied potential differences as compared to healthy persons. Moreover, we explored if patients with different underlying neurological pathologies differ in profile scores on the SCL-90-R, while we expected that specific neurological diseases might result in diverse complaints. We expected, for example, that patients with cerebrovascular disease would have higher scores on the somatic scale because of their physical problems (20), and that patients with traumatic brain injury would have high scores the hostility scale because of the abrupt psychosocial changes they underwent (e.g. 21). Finally, we discuss the benefit of normative data for a neurological group. In many (psychiatric) clinical settings it is common practice to compare a patient's score on the SCL-90-R firstly to normative data of healthy control subjects, and secondly to normative data of a psychiatric sample. The rationale for

this approach is that psychiatric patients can have such high scores that a ceiling effect arises when the scores are only compared to those of healthy control subjects. When comparing a psychiatric patient also to normative data from a comparable psychiatric group, more differentiations in the SCL-90 profile can be made. Such a two-step procedure may also be workable for specific neurological normative data.

Methods

Questionnaire

In this study the Dutch version of the SCL-90-R (22,23) was used. This version of the questionnaire is based on the SCL-90-R of Derogatis (3,4). The questionnaire consists of 90 items rated on a five-point Likert scale (1= no complaints at all, 5= high level of complaints). In contrast to the original version of the SCL-90-R the items are clustered in eight instead of nine subscales. The subscales (based on factor analysis with VARIMAX rotation) are defined as *Anxiety* (ANX), *Agoraphobia* (AGO) (in original version *Phobic Anxiety*, PHOB), *Somatic Symptoms* (SOM), *Depression* (DEP), *Inadequacy of Thinking and Acting* (IN) (in original version *Obsessive-Compulsive*, O-C), *Distrust and Interpersonal Sensitivity* (SEN), *Hostility* (HOS) and *Sleeping Problems* (SLE) (23). Adding these subscales together results in a general measure of psychoneurotic-somatic distress (PSNEUR). Maximum scores on the subscales differ from 15 to 90. In the Dutch version of the questionnaire items of the original subscales *Interpersonal Sensitivity* (I-S), *Paranoid Ideation* (PAR) and *Psychoticism* (PSY) are combined in the subscale SEN. Furthermore, in the Dutch version an additional scale is described, namely SLE. There are only slight differences in item assignment to the other subscales in the Dutch and the original version of the SCL-90-R.

The Dutch version of the SCL-90-R provides normative data for healthy control subjects (*n*=2368) and psychiatric outpatients (*n*=5658). In addition, normative data are collected for chronic pain patients (*n*=2458), patients treated for substance abuse (*n*=1574), clients from a (primary care) psychological practice (*n*=711) and patients from a general medical practice (*n*=957) (23). The amount and pattern of complaints in all these groups is different. The normative data of the healthy control subjects will be used in our analysis. As mentioned before, in clinical practice scores on the SCL-90-R are often compared with both healthy control subjects as with the psychiatric normative sample. Therefore, the data of this latter group is also shown in the figures as an illustration.

Study population

Patients included in this study visited the neurological outpatient clinic of the University Medical Center Utrecht in the Netherlands between 2003 and 2012 and were referred for a (first ever) neuropsychological assessment (*N*=600). All patients were native Dutch speaking or were able to speak and comprehend the Dutch language on an adequate level in order to fill out the SCL-90-R. Patients with reading difficulties of other problems that could be blurring the test scores of the questionnaire were excluded. The mean age of our patient group was 51.7 (*SD* 15.2) years, and 58% was male. Mean years of education were 10.7 (*SD* 2.7).

The patients included in this study were either diagnosed with or suspected for a neurological disease. The total population was subdivided according to eleven categories of disorders, based on the primary diagnosis of the neurologist following neuropsychological assessment, mostly within a few weeks. Detailed information about these categories is shown in table 1.

Statistical analysis

In the primary analysis the neurological patient group is compared with the published normative data (mean and standard deviation) of the healthy control group (23). The statistical program MetaAnalyst is used for this analysis *t*-tests and effect sizes (Hedge's g, based on pooled variance) a))) are calculated. In secondary analysis the five most homogeneous subgroups with the largest sample size (*neurodegenerative disease*, *cerebrovascular disease*, *epilepsy*, *brain tumor* and *traumatic brain injury)* (see table 2 for details of mean age, mean level of education and percentage males in these groups) are compared with healthy control subjects. Furthermore, multivariate analysis of variance (SPSS 20) was used to further contrast these subgroups to analyse whether a specific neurological disease results in a particular profile of complaints. The data of the remaining categories (*autoimmune disease*, *infectious disease*, *neurological disorder e.c.i.*, *no neurological disease*, *psychological problems* and *other neurological disease)* were not included in these analyses because of limited group size or heterogeneity.

Table 1 Categories of disorders and examples of diseases assigned to these categories (based on the primary diagnosis of the neurologist following neuropsychological assessment).

Category	Diseases	*n*
Neurodegenerative disease	Alzheimer's disease, Fronto Temporal Dementia, Primary Progressive Aphasia, vascular dementia, Mild Cognitive Impairment (MCI), Parkinson's disease, corticobasal degeneration, Huntington's disease, Lewy Body dementia, Amiotrophic Lateral Sclerosis (ALS)	106
Cerebrovascular disease	Ischemic stroke, hemmorhagic stroke, Transient Ischemic Attack (TIA), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), subarachnoid hemmorhage, white matter abnormalities, Moya Moya disease	85
Traumatic brain injury	Commotio cerebri, contusio cerebri	60
Brain tumor	Glioma, meningeoma, blastoma, adenoma, lymphoma, hemangioma, astrocystoma	50
Epilepsy	Idiopathic and cryptogenic forms of epilepsy	33
Autoimmune disease	Multiple Sclerose, Hashimoto encephalopathy, Hashimoto thyroiditis, Systemic Lupus Erythematosus (SLE), Wegener disease	17
Infectious disease	Encephalopathy, meningitis, neuroborreliosis, Human Immunodeficiency Virus (HIV), neurolues	15
Neurological disorder e.c.i.	Etiology unknown, further investigations needed	70
No neurological disease	No cognitive disorders could be identified and there is no (suspicion of) neurological disease (patients were sent home)	50
Psychological problems	Depression, anxiety, functional disorder, burn-out, personality disorder	75
Other disorder	Normal Pressure Hydrocephalus, Attention Deficit Hyperactivity Disorder, vitamine B12 deficiency, type 1 diabetes mellitus, alcohol abuse	39

Table 2 Mean age, mean years of education and % male of the five main neurological categories.

Characteristic	Neurodegenerative disease	Cerebrovascular disease	Traumatic brain injury	Brain tumor	Epilepsy
Mean age	66.0 (8.6)	52.5 (13.1)	41.9 (15.0)	42.9 (13.6)	44.2 (17.5)
Mean years of education	10.9 (2.6)	10.9 (2.7)	10.4 (3.0)	11.1 (2.5)	10.7 (2.4)
% Male	67	48	68	58	55

Results

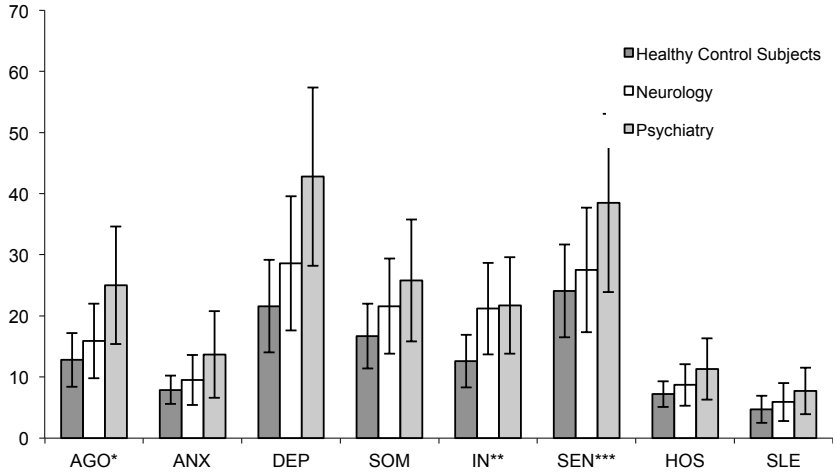
The neurological outpatients reported significantly more complaints than the healthy control subjects (total score: PSNEUR, *t* (2966) =20.58, *p*<.01) and all subscales were significantly higher in neurological patients (*p*<.01). Effects sizes varied from moderate to large (.41 to 1.69), largest effect sizes were found for the subscales IN (1.69), DEP (.83) and SOM (.83) (see table 3 and figure 1). While the scores of the neurological patient group were elevated in comparison with the healthy control group, the scores were lower than those of the psychiatric patient group (an also frequently used normative data group). The overall pattern (profile of high and low scores) was highly comparable between the three groups.

Table 3 Mean and SD on subscales of SCL-90-R from healthy control subjects and neurological outpatients, statistical data of the t-tests (t, p and effect size).

Subscale	Healthy control subjects	Neurology	*t*	*p*	Effect size
AGO	12.8 (4.4)	15.9 (6.1)	14.2	<.01	0.65
ANX	7.9 (2.3)	9.5 (4.1)	12.7	<.01	0.58
DEP	21.6 (7.6)	28.6 (11.0)	18.2	<.01	0.83
SOM	16.7 (5.3)	21.6 (7.8)	18.2	<.01	0.83
IN	12.6 (4.3)	21.2 (7.5)	36.8	<.01	1.69
SEN	24.1 (7.6)	27.5 (10.2)	9.1	<.01	0.41
HOS	7.2 (2.1)	8.7 (3.4)	13.6	<.01	0.62
SLE	4.7 (2.2)	5.9 (3.1)	10.9	<.01	0.50

When comparing the scores of the five main neurological pathologies on the SCL-90-R with the scores of the healthy control subjects, the level of complaints was elevated on all subscales of all patient groups (*p*<.01, except for subscale SLE in patients with brain tumors: *p* =.05; effect sizes .09-1.74) (see table 4). Moreover, the overall pattern of each individual diagnostic subgroup was highly similar to the neurological population in general and the between-group differences were not statistically significant (see figure 2), except the subscale HOS (*F*=2.48, *p*=.04) which was higher in traumatic brain injury than in neurodegenerative disease (mean difference raw scores 1.42, *p*=.07).

Figure 1 Mean scores on the subscales of the SCL-90-R of a healthy control group, neurological outpatients and psychiatric outpatients.

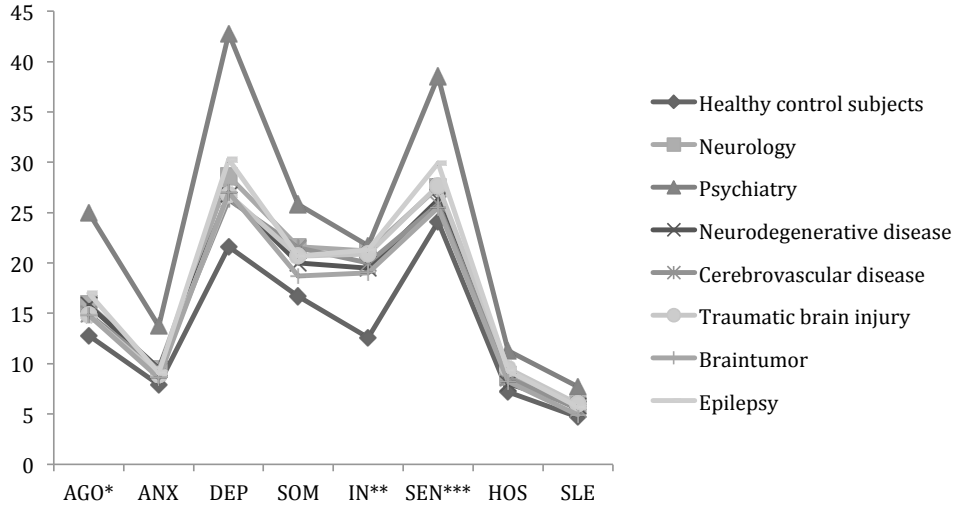


AGO: Agoraphobia, ANX: Anxiety, DEP: Depression, SOM: Somatic Symptoms, IN: Inadequacy of Thinking and Acting, SEN: Distrust and Interpersonal Sensitivity, HOS: Hostility, SLE: Sleeping Problems.
* Corresponding to original subscale Phobic Anxiety
** Corresponding to original subscale Obsessive-Compulsive
*** Corresponding to original subscales Interpersonal Sensitivity, Paranoid Ideation and Psychoticism

Table 4 Mean and SD on subscales of SCL-90-R from five main neurological categories.

Subscale	Neurodegenerative disease	Cerebrovascular disease	Traumatic brain injury	Brain tumor	Epilepsy
AGO	15.8 (6.2)	14.9 (5.4)	14.8 (5.9)	14.8 (5.4)	17.0 (6.7)
ANX	9.5 (4.3)	9.4 (4.0)	8.9 (3.6)	8.6 (2.2)	9.1 (2.8)
DEP	26.8 (9.3)	26.3 (9.9)	28.6 (12.2)	27.0 (9.3)	30.3 (11.0)
SOM	20.0 (7.1)	21.5 (8.0)	20.7 (7.5)	18.7 (6.7)	20.7 (7.3)
IN	19.5 (7.1)	20.0 (7.5)	20.9 (7.5)	19.0 (7.2)	21.3 (7.1)
SEN	26.3 (10.1)	25.8 (9.5)	27.7 (11.0)	25.5 (8.5)	29.9 (10.6)
HOS	8.0 (2.6)	8.6 (3.6)	9.5 (4.0)	8.2 (2.6)	9.3 (3.3)
SLE	5.8 (3.1)	5.5 (3.1)	6.0 (3.2)	4.9 (2.2)	5.7 (2.8)

Figure 2 Pattern of scores on the SCL-90-R of neurological outpatients, psychiatric outpatients, a healthy control group and the five main neurological categories.



AGO: Agoraphobia, ANX: Anxiety, DEP: Depression, SOM: Somatic Symptoms, IN: Inadequacy of Thinking and Acting, SEN: Distrust and Interpersonal Sensitivity, HOS: Hostility, SLE: Sleeping Problems.
* Corresponding to original subscale Phobic Anxiety
** Corresponding to original subscale Obsessive-Compulsive
*** Corresponding to original subscales Interpersonal Sensitivity, Paranoid Ideation and Psychoticism

The other categories (*autoimmune disease*, *infectious disease*, *neurological disorder e.c.i.*, *no neurological disease*, *psychological problems* and *other neurological disease)* showed the same pattern as the neurological population in general. In all categories, the scores on the subscales lied between the healthy control subjects and the psychiatric group, except for the subscale IN in the category *Psychological problems*, which was above the mean score of the psychiatric population.

Discussion

The aim of this study was to analyse the response patterns of a large sample of neurological outpatients on the SCL-90-R. Furthermore, we wanted to compare the scores of different neurological patient groups. In light of the previous literature on this issue we wanted to discuss the use of normative data of healthy control subjects in a neurological outpatient population.

The present study demonstrates that a neurological patient group has a significantly higher level of complaints than a healthy control group. Especially the subscales IN, DEP and SOM

were elevated in our patient group. Interestingly, we did not found any differences between the various neurological pathologies. Our hypothesis that different neurological diseases would result in different complaints as measured by the SCL-90-R was rejected. The fact that there are no differences in scores between various neurological pathologies from which a patient suffers, suggest that suffering from a neurological disorder in itself is determinative and not the specific disease.

Results of our study are supported by findings of previous studies. Studies in specific neurological patients groups founded higher scores on the subscales SOM, IN (O-C) and DEP and to a lesser extent on the subscales HOS, AGO (PHOB) and SEN (I-S/PAR/PSY) (12,15,16,19). This is in line with our results in a general neurological population.

Because neurological patients have significantly more complaints than a healthy control group, they cannot be simply compared with the existing normative data. According to the manual, 6 out of 8 subscale scores of the neurological patients in this study will be labelled as *above average*, *high* or *very high* when compared to normative data from healthy participants. This means that their scores range from 1 SD above the mean to above the 95th percentile, which is clearly in a clinically significant range. Nevertheless, patients with neurological diseases may have more cognitive, somatic or emotional complaints than healthy persons, maybe not as a result of psychological symptoms but as a direct or indirect consequence of their neurological condition. Elevated scores can also reflect somatic problems directly as a result of a medical disease. Furthermore, they can reflect damage to brain structures (for example in areas involved in emotions) or symptoms related to adjusting to a medical disease. Conventional interpretation of the SCL-90-R scores in neurological outpatients could therefore cause inappropriate classifications with regard to the measurement of psychopathology. Interpretation of the elevated scores is difficult and psychiatric and neurological causes cannot not be pulled apart strictly, moreover because neurological disorders can be accompanied by psychiatric problems such as depression. Although interpretation should be done with high caution, we briefly discuss some possible causes of the high scores. It would be plausible to assume that the high score of our patients on IN is the result of the cognitive impairments neurological patients experience. For example, one of the items of this subscale asks a patient if he/she has difficulties remembering something. However, previous research of Kaplan and Miner (24) in a group of patients with a brain tumor showed that this subscale is not related to cognitive impairments as measured with a neuropsychological assessment. On the other hand, their analyses revealed a significant relation of this subscale to symptoms of depression, anxiety, and *subjective* complaints of memory problems. Kaplan and Miner suggest that this subscale should be viewed as an indicator of general emotional distress. In our view, confrontation with a (in some cases life-

threatening) neurological disease and the constraints that follow can cause a high amount of emotional distress, in many cases even depressive symptoms. This can be an explanation of the high scores on the subscales IN and DEP. Furthermore; neurological diseases are often accompanied by somatic complaints. For example, such a common complaint as headache is associated with many neurological diseases such as stroke (25) and brain tumors (26,27). Other somatic complaints (e.g. nausea) are, amongst other symptoms, associated with for example traumatic brain injury (e.g. 28). It is plausible that in our patient group this type of complaints and their high score on the subscale SOM are the result of the neurological disease instead of an expression of psychological stress. When we assume that these complaints are most likely disease-related symptoms, those should be interpreted as a result of the neurological condition and not as a part of psychopathology.

Interestingly, while our patient sample showed higher scores on all subscales, the pattern of scores on the difference subscales was highly similar to the pattern observed in healthy control subjects. This has important clinical consequences: when interpreting this questionnaire in neurological patients we should not oversimplify and attribute *all* of their complaints directly to the disease they suffer from. When one or two of the subscales are evidently elevated in comparison with the other subscales these scores should be analyzed carefully.

We underline that interpretation of the SCL-90-R scores should be done with high caution. As suggested previously by authors of other studies multiple sources of information (interview, observations) should be taken into account in the measurement of psychopathology in brain-injured patients. This is similar for the use of, for example, the MMPI in neurological patients, whereas special administrative and interpretative considerations are needed (29). Future research at item level may contribute in this discussion, although these kinds of analyses also hold several restrictions as described previous by Kaplan (13).

Several limitations of the present study need to be discussed. The results of this study only describe the symptoms of Dutch patients and could not be simply generalised to all other cultures. The way and level on which people complain is dependent on cultural differences. On the other hand, we assume that there are no large differences between other (western) cultures in comparing a patient group to a healthy control group.

Another limitation may be the slight differences between the Dutch version of the SCL-90-R and the original version. Albeit a somewhat different factor structure, we think the questionnaires are highly comparable. The subscales have a high similarity and the items used in both lists are identical.

Our patient population is a selection of a general neurological population because all patients were referred for a neuropsychological assessment and thus suspected for cognitive problems. Although this may sound as a constriction, these are exactly the patients for who this discussion is worth full. Another potential limitation is that some patients may suffer from more than one disease, thereby blurring the secondary analyses. Moreover, several patients may suffer from diseases other than neurological and it is also possible that patients who visited the neurological outpatient clinic are eventually not diagnosed with the neurological disease that was initially suspected or diagnosed. Similar limitations hold for other published normative data for the SCL-90-R. For example, normative data for psychiatric patients in the Netherlands are based upon patients who visited the psychiatric outpatient clinic for the first time.

The scores of individual patients on the SCL-90-R may have influenced the diagnosis of the neurologist in some cases (for example in patients assigned to the category *Psychological Problems*). However, as the neurological diagnosis is reached by a combination of neurological examinations, imaging techniques, laboratory investigations and neuropsychological assessments, we feel that, at least for the five main categories, this circular reasoning does not play a role.

A noteworthy strength of our study is the large sample of patients, which also allows for reliable examination and comparison of several subgroups of patients with a particular type of disease.

The current data can be used as normative data for the Dutch population. Collecting normative data for other countries would be contributing. The use of additional normative data (as previous suggested by i.a. Kaplan et al. (12)) and more knowledge about the elevated pattern of scores on the SCL-90-R of neurological outpatients makes clinicians more aware of possible inappropriate classifications of the complaints and symptoms of this population. In many clinical psychiatric settings it is common practice to compare a patients score first to the healthy control group and secondly to the psychiatric normative data. This method could also be useful in using additional normative data for neurological patients. Scores of neurological patients should first be compared with the existing normative data from healthy control subjects. After that, scores can be compared with neurological normative data so that clinicians can analyse if the overall pattern is elevated or that specific subscales stand out. As a result, a better interpretation of the complaints of those patients can be made.

References

1. Derogatis, L.R., Lipman, R.S., & Covi, L. (1973). SCL-90: an outpatient psychiatric rating scale – preliminary report. *Psychopharmacology Bulletin, 9*, 13-27.
2. Piotrowski, C., & Lubin, B. (1990). Assessment practices of health psychologists: survey of APA division 38 clinicians. *Professional Psychology: Research and Practice, 21 (*2), 99-106.
3. Derogatis, L.R. (1977). *SCL-90: administration, scoring and procedures manual-I for the R(evised) version*. Baltimore: Johns Hopkins University School of Medicine, Clinical Psychometrics Research Unit.
4. Derogatis, L.R. (1994). *SCL-90-R: administration, scoring and procedures manual. Third edition*. Minneapolis, MN: Nation Computer Systems.
5. Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (2012). *Tests of personal adjustment and emotional functioning*. In Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (eds), Neuropsychological Assessment (pp 804-829). New York: Oxford U.P.
6. Leon-Carrion, J., Taaffe, P.J., & Barroso y Martin, J.M. (2006). *Neuropsychological assessment of persons with acquired brain injury.* In Leon-Carrion, J., von Wild, K.R.H., & Zitnay, G.A. (eds), Brain injury treatment: Theories and practices (pp 275-310). New York: Taylor & Francis.
7. Weingartner, H., Cohen, R.M., Murphy, D.L., Martello, J., & Gerdt, C. (1981). Cognitive processes in depression. *Archives of General Psychiatry, 38*, 42-47.
8. Alfano, D.P., Finlayson, A.J., Stearns, G.M., & Neilson, P.M. (1990). The MMPI and neurologic dysfunction: Profile configuration and analysis. *Clinical Neuropsychologist, 4*, 69-79.
9. Bornstein, R.A., & Kozora, E. (1990). Content bias of the MMPI Sc scale in neurological patients. *Cognitive and Behavioural Neurology, 3*, 200-205.
10. Alfano, D.P., Paniak, C. E., & Finlayson, M.A. (1993). The MMPI and closed head injury: a neurocorrective approach. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 6,* 111-116.
11. Glassmire, D.M., Kinney, D.I., Greene, R.L., Stolberg, R.A., Berry, D.T.R., & Cripe, L. (2003). Sensitivity and specificity of MMPI-2 neurologic correction factors: receiver operating characteristic analysis. *Assessment, 10* (3), 299-309.
12. Kaplan, C.P., Miner, M.E., Mervis, L., Newton, H., McGregor, J.M., & Goodman, J. H. (1998). Interpretive risks: the use of the Hopkins Symptom Checklist 90-Revised (SCL 90-R) with brain tumour patients. *Brain Injury*, *12*, 199-205.
13. Kaplan, C. P. (1998). SCL 90-R interpretation and brain tumour: a correction factor? *Brain Injury*, *12*, 977-985.
14. Gass, C.S., & Wald, H.S. (1997). MMPI-2 interpretation and closed-head trauma: cross-validation of a correction factor. *Archives of Clinical Neuropsychology, 12*, 199-205.
15. Tate, D. G., Kewman, D.G., & Maynard, F. (1990). The Brief Symptom Inventory: measuring psychological distress in spinal cord injury. *Rehabilitation Psychology, 35*, 211-216.
16. Woessner, R., & Caplan, B. (1995). Affective disorders following mild to moderate brain injury: interpretive hazards of the SCL-90-R. *Journal of Head Trauma Rehabilitation, 10*, 78-89.
17. Leathem, J.M., & Babbage, D.R. (2000). Affective disorders after traumatic brain injury: cautions in the use of the Symptom Checklist-90-R. *Journal of Head Trauma Rehabilitation, 15* (6), 1246-1255.
18. Caplan, B., & Woessner, R. (1992). Psychopathology following head trauma? Interpretive hazards of the Symptom Checklist-90-revised (SCL-90). *Journal of Clinical and Experimental Neuropsychology, 14*, 78.

19. Woessner, R., & Caplan, B. (1996) Emotional distress following stroke: interpretive limitations of the SCL-90-R. *Assessment, 3*, 291-305.
20. Warlow, C. P., Van Gijn, J., Dennis, M. S., Wardlaw, J. M., Bamford, J. M., Hankey, G. J.,Sandercock, P., Rinkel, G., Langhorne, P., Sudlow, C., & Rothwell, P. (2011). *Stroke: practical management*. Hoboken, NJ: John Wiley & Sons.
21. Baguley, IJ., Cooper, J., & Felmingham, K.L. (2006). Aggressive behaviour following traumatic brain injury. *Journal of Head Trauma Rehabilitation, 21 (1),* 45-56.
22. Arrindell, W.A., & Ettema, J.H.M. (1986). *Symptom Checklist. Handleiding bij een multidimensionale psychopathologie-indicator* (Dutch). Lisse, the Netherlands: Swets & Zeitlinger.
23. Arrindell, W.A., & Ettema, J.H.M. (2005). *Symptom Checklist. Handleiding bij een multidimensionale psychopathologie-indicator* (Dutch). Amsterdam, the Netherlands: Harcourt Test Publishers.
24. Kaplan, C.P., & Miner, M.E. (1998). Does the SCL-90-R obsessive-compulsive dimension identity cognitive impairments? *Journal of Head Trauma Rehabilitation, 13*, 94-101.
25. Stang, P.E., Carson, A.P., Rose, K.M., Mo, J., Ephross, S.A., Sharar, E., & Szklo, M. (2005). Headache, cerebrovascular symptoms, and stroke. The Atherosclerosis Risk in Communities Study. *Neurology, 64*, 1573-1577.
26. Forsyth, P.A., & Posner, J.B. (1993). Headaches in patients with brain tumors. A study of 111 patients. *Neurology, 43*, 1678.
27. Schankin, C.J., Ferrari, U., Reinisch, V.M, Birnbaum, T., Goldbrunner, R., & Straube, A. (2007). Characteristics of brain tumour-associated headache. *Cephalalgia, 27*, 904-911.
28. De Kruijk, J.R., Leffers, P., Menheere, P.P.C.A., Meerhoff, S., Rutten, J., & Twijnstra, A. (2002). Prediction of post-traumatic complaints after mild traumatic brain injury: early symptoms and biochemical markers. *Journal of Neurology, Neurosurgery & Psychiatry, 73*, 727-732.
29. Gass, C.S. (2009). *Use of the MMPI-2 in neuropsychological evaluation*. In: Butcher, J.N. (ed), Oxford handbook of personality assessment (pp 432-456). Oxford, NY: Oxford University Press.

CHAPTER 5

Awake craniotomy and coaching

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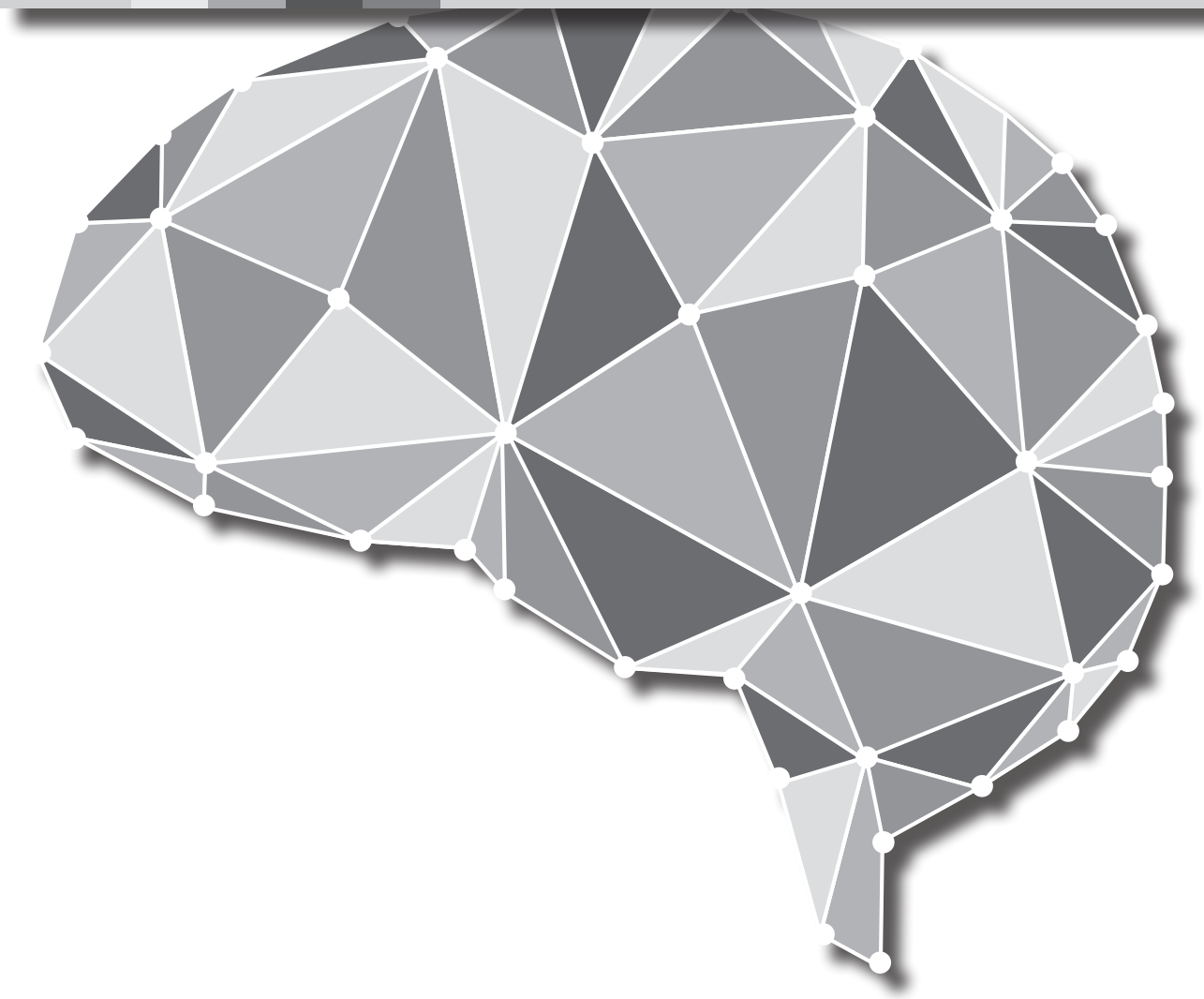
Submitted



Abstract

The importance of monitoring cognition during awake craniotomy has been well described in previous studies. The relevance of being coached during such a procedure has received less attention and questions about what factors are most important herein remains still unanswered.

Twenty-six patients who underwent awake craniotomy received a questionnaire about their experiences during the procedure. The questions concerned different aspects of the pre-operative part, the operation itself and coaching aspects.

Two thirds of the twenty patients who responded to the questionnaire reported anxiety in the days before or during the operation, varying from general anxiety for being awake during surgery to anxiety for very specific aspects. The constant presence of the neuropsychologist and a transparent communication were reported as helpful in staying calm.

Results of this descriptive study underline that coaching is important for patients and it enables valid cognitive monitoring during awake craniotomy. This study provides handhelds for clinicians in improving their role as a coach.

Introduction

The purpose of awake craniotomy is to monitor the activity of eloquent brain areas while removing tumors or other lesions that are located in them. This helps to maximize the resection, while preserving neurological functions and quality of life (1-3). Intraoperative mapping was first described and performed around 1900 by Cushing (4) and later by Penfield (5). The last decades intraoperative mapping was mostly used to monitor motor and language functions (6). More recently, interest in monitoring other cognitive functions as well during the awake procedure is growing (7-9).

Literature research shows that most studies about awake craniotomy do mention the importance of measuring cognition, mostly done by a neuropsychologist (3,8). Lesser studies analysed patient tolerance and acceptance of awake craniotomy (10,11). These studies indicate that patients are comfortable with the experience and show good acceptance of the procedure. Other studies analysed patients' experiences and perceptions. Those studies give more insight in the feelings patients experienced immediately before, during and after the awake surgery (12) and show that most patients experienced awake craniotomy as positive (13), although other studies (e.g. 14) indicate that patients can also be anxious during the operation. Questions how to handle these anxieties and how to coach a patient during craniotomy has been underexposed.

We believe that several aspects and causes of patients' awake craniotomy related anxieties are amenable to coaching. Based on this assumption, in our clinic, we followed multiple coaching interventions before and during the awake surgical procedures as building a trustful relation between patient and neuropsychologist, providing comprehensive information about the procedure, teaching relaxation by means of breathing exercises, and providing support and encouragement. To verify our ideas and to fine-tune our role as a coach we asked our patients about their experiences in two parts of the procedure wherein coaching is highly important, namely the pre-operative stage and during the procedure. Furthermore, we asked them about aspects of reassurance during the complete procedure. This paper describes patients' responses to the questionnaire.

Methods

This study was approved by the local medical ethic committee. Results of this study were analysed anonymously.

Patients

Twenty-six patients were included in this study. All patients underwent awake craniotomy between 2012 and 2013 because of a primary brain tumor. Time between craniotomy and enrolment in the study ranged between one and eleven months.

Procedures pre-operative

All patients had an extensive work-up before the operation. The neurosurgeon, nurse practitioner and neuropsychologist, explained the procedures out of their own expertise. The explanation of the neuropsychologist consisted of multifaceted components, subdivided in clarifications about the procedure, communication style during the operation, coping with anxiety and emotions, relaxation techniques (breathing exercises and principles of the cognitive behavioural therapy), and expectations for the future. Thereafter, the neuropsychologist administrated a neuropsychological assessment, existing of standard neuropsychological tests. In addition, specific testing paradigms according to the procedures during the surgery concerning language, working memory, executive functioning (inhibition), visuoperception, sensory motor functions and parietal functions such as calculation were administrated.

Surgical procedures

Patients were operated under local anesthesia, microscope view and ultrasound and neuronavigation guidance. The procedures were performed in a parkbench position, allowing the patients to relax and to face the neuropsychologist in a comfortable fashion. The head was fixed in a Mayfield clamp. Local anesthesia was obtained using a mix of 5mg/ml chirocaine 1:1 v:v and 2% lidocaine with adrenaline 1:200,000 (a total of 32-55cc for the complete procedure) injected at the pin sites of the Mayfield clamp and in a rectangular fashion around the planned skin incision site. After removal of the bone flap, a local application of the anesthetics mix was also applied onto the dura at the level of the meningeal arteries. Patients also benefited from titrated pain sedation and relaxation with remifentanyl and propofol, respectively. Craniotomies were performed using Anspach® high-speed drills and craniotomes, and tumors were removed using conventional microneurosurgical techniques and under constant cortico-subcortical stimulations using a Micromed® cortical stimulator (50Hz, 1ms, 2-5 mAmps, trains of 3 seconds at the cortical level and continuous stimulations at the subcortical level). None of the patients had to be returned to general anaesthesia.

Monitoring of the cognitive status by means of cognitive tests administrated by the neuropsychologist was feasible in all patients. The order of tasks was dependent on the location of the stimulation and the condition of the patient. Between testing the neuropsychologist and patient talked about different pre-arranged topics of patient's

interest. The neurosurgeon and the neuropsychologist continuously explained to the patient what was happening. When a patient panicked or experienced pain, breathing exercises were used. Patients were motivated and stimulated to keep up their motivation for the ongoing operation. The neuropsychologist sat right next to the patient and was present from start till the end of the craniotomy.

Questionnaire

Patients were asked to answer five open questions send by letter, about experiences during the pre-operative part, the operation itself and coaching aspects.

The questionnaire consisted of the following questions:

Pre-operative part

Can you indicate how much information you wanted to have about the operation?

What worried you the most in the days before the operation?

During the operation

Which moments during the operation were frightening for you?

How did you experience it to be tested during the operation?

Coaching

Where there specific things during the explanation about the procedure and during the operation itself that made you more at ease?

Results

Patients

Twenty of the 26 patients (77%) returned the questionnaire. There were no differences in mean age or phase of treatment between the patients who did responded to the questionnaire in comparison to those who did not. Out of the twenty patients who responded 9 patients were suspected for a low-grade tumor, 11 were suspected for a high-grade tumor (suspected pathology before craniotomy). Mean age of the total group was 52.0 years (range 28-78), and 55 % were male.

Questionnaire

The answers of our patients were categorized per question (see table 1).

Table 1 Responses of the total patient sample on the questionnaire about the pre-operative part (question 1 and 2), the operation (question 3 and 4) and coaching aspects (question 5) of an awake craniotomy (*N*=20).

	Percentage	***n***
Can you indicate how much information you wanted to have about the operation?		
As much information as possible	45%	9
Just the most important things, no details	30%	6
As little information as possible	5%	1
Other answers	20%	4
What worried you the most in the days before the operation?		
I had no worries	35%	7
Being awake in general	20%	4
That I would panic	15%	3
That complications would arise	10%	2
Specific other things (e.g. opening the skull)	10%	2
Other answers	10%	2
Which moments during the operation were frightening for you?		
No moments of increased anxiety	35%	7
Other specific moments (e.g. epileptic attack, shaking of the body, lowering of blood pressure)	30%	6
When I was having pain	15%	3
Being in the same position for a long period	15%	3
Other answers	5%	1
How did you experience it to be tested during the operation?		
Positive	65%	13
It distracted me from the operation	15%	3
Wearily	10%	2
Other answers	10%	2
Where there specific things during the explanation about the procedure and during the operation itself that made you more at ease?		
Constant support of neuropsychologist	40%	8
Transparent manner of communicating, relaxed atmosphere	25%	5
Relation with neuropsychologist	5%	1
Clear explanations	5%	1
Conformation that I did it well (reassurance)	5%	1
Other answers	20%	4

Pre-operative part

Results of the questionnaire show that 45% of the patients wanted to receive as much information as possible ("*I wanted to know exactly what was going to happen and how long it would take"*). The majority of patients (55%) wanted to receive information about the procedure in a variable degree (e.g. "*I wanted to know the most important things but I did not want to know any details*"). One of the patients reported that the operation was not his primary concern ("*I was so much thinking about the consequences of the procedure that the operation itself seemed secondary*").

Similarly, patients responded very different when asked what aspects of the procedure frightened them most in the days before the operation. Thirty-five per cent of our patients did not have any specific worries. The ones who did worried were scared for the procedure in general ("*It was frightening for me to stay awake during the procedure*") (20%), or were afraid to lose control ("*I was afraid to lose control and to panic*", "*I thought I was not able to manage it*") (15%). Others were scared of complications ("*I was afraid that they would damage something in my head*") or reported very specific anxieties ("*The most frightening part for me was the part where they had to saw*").

<u>During the operation</u>

When asked about moments during the operation when the anxiety level increased, one out of every three patients indicated that these moments did not occur. Conversely, specific events such *"having an epileptic insult*" or "*shaking of the body*" were experienced as very anxious (30%). Other anxious moments were related to pain or discomfort ("*opening the skull was very painful*", "*when I experienced pain I kind of panicked*", "*lying in the same position for a long period was hard to maintain*") (30%).

The administration of tests during the operation was positively evaluated by almost all of our patients. Testing made them not continuously busy with the operation ("*I was distracted and this was nice*"). Only two out of twenty patients experienced the testing part as wearily.

<u>Coaching</u>

When patients were asked what made them more at ease in the days before the operation and during the procedure itself, almost half of them indicated that the intensive contact with the neuropsychologist was very important. Frequently given answers were "*I was more at ease because I knew someone was right next to me all the time*", "*It was pleasant that we had constantly contact*", or "*It was pleasant that I had met the neuropsychologist several times before the operation*". The atmosphere in the operation room was likewise important for our patients ("*the open manner of communicating was nice, even as the equivalency*", "*the relaxed atmosphere was restful*") (25%). Apparently unimportant small things were also reported as being of high value, as in *"it was comforting that the neuropsychologist was constantly holding my hand"*.

Notably, there were no differences between patients with suspected low (*n*=9) or high-grade tumors (*n*=11), low (<50 years, *n*=9) or high age (>50 years, *n*=11) and time between the operation and receiving the questionnaire (1-4 months, *n*=10 versus 5-11 months, *n*=10) in the amount of information they wanted to receive. Similarly, there were no differences between those groups in the experiences to be tested during an operation and in the aspects that were mentioned as reassuring. However, there were differences between the groups

in the amount of reported anxieties. Nearly all patients with a suspected low-grade tumor described anxieties in the days before the operation (almost 90% of them). Surprisingly, less than half of the patients with a suspected high-grade tumor reported anxieties (45%). Furthermore, in the group of younger patients more anxieties were reported (almost 90%) than in older patients (45%). Finally, patients who underwent the operation more recently described more anxieties (90%) than patients for whom the operation was longer ago (45%).

Discussion

The importance of measuring cognition during awake craniotomy is well described (e.g. 3,8), but coaching aspects during the pre-operative phase and during the operation has been underexposed. Studies that do mention the coaching aspect describe it as separate from the cognitive measurements and as the responsibility of a social worker (15). In this study we wanted to explore what aspects are most important in coaching according to our patients.

In the pre-operative stage patients differ greatly in the amount of information they wanted to receive about the operation. Nearly half of the people wanted to know in detail what was going to happen, while one third of the patients stated not to be in need of detailed information at forehand. Although adjustment of the amount of information in individual cases is good, a minimal amount of information is required. Patients have to know the outlines of what is expected from them and a concrete preparation can be helpful in reducing anxiety levels (16).

With regard to experienced anxiety in the pre-operative stage, it appeared that patients were frightened for very different things. Some patients were anxious for being awake in general, whereas others reported anxiety for very specific things, such as opening the skull. Clinicians should ask about these fears so that possible misperceptions can be prevented and more explanations can be given.

During the operation the amount of anxiety increased in some patients when they experienced pain or discomfort. Explaining what causes the pain can be helpful even as coaching a patient in coping with it. Our patients did not specifically mention breathing exercises as being helpful.

Two out of every three of our patients were positive about being tested during the operation. Some of them indicated that it distracted them from what was actually happening in the

operation room and they experienced this as pleasant. Only two out of the twenty patients explicitly stated that testing wear them off.

When asked about coaching aspects, patients were most reassured by the idea that someone was there for them during the whole procedure. Moreover, an open and transparent manner of communicating was also helpful for our patients. Finally, small things such as holding someone's hand seemed to be of great value.

Notably, our questionnaire revealed that patients who underwent the operation more recently reported more anxieties than patients for whom the operation was already longer ago. This might be due to the fact that negative experiences disappear more to the background as a result of a developing acceptance of the procedure and the situation of having a brain tumor. Furthermore, older patients reported less anxiety than younger patients, which is in line of what was expected, as in general, anxiety declines with age (17). In our patient sample we also found differences between patients with a suspected low and high-grade tumor, in which patients with a suspected low-grade tumor reported more anxieties. However, ten out of eleven patients with a high-grade tumor were aged above fifty, so the effect of age may bias this result. In a previous study of d'Angelo et al. (18) no differences in state anxiety in patients with low or high-grade tumors was found. Nevertheless, future research studying the relation between low and high-grade tumors and coaching aspects would be interesting.

The results of this study are mainly in line with our assumptions, based on experiences of previous operations on how to coach a patient during awake craniotomy. Nevertheless, results of the questionnaire made clear what aspects are most important in coaching someone, according to our patients. Specific things, such as being constantly there for your patient, turned out to be of much more meaning than previously expected and other things, such as breathing techniques, were less important in the view of our patients. One of the most essential aspects revealed by this study is the relevance of an intensive relation between the neuropsychologist and the patient, while this was reported as most reassuring. Patients indicate that talking to them, explaining what is happening and coaching them when they are panicking or having pain, are highly important. Investigating time in a trustful relationship with your patient appears to be of great relevance.

In line with previous literature about patients' perceptions and acceptance of this kind of procedure (11,13), most of our patients experienced the awake craniotomy as positive. Nevertheless, our study revealed also anxieties that need special attention. In addition, pain and discomfort during the operation resulted as well in moments of increased anxiety. Since

most of these physical discomforts are inevitable, these results underline the importance of being coached during awake craniotomy.

A valid and reliable manner of monitoring cognition is highly dependent on the patient being calm and not bothered by anxieties. To our opinion, monitoring cognition and coaching a patient cannot be seen as two separate tasks, because of the interaction between anxiety and test performance. When a patient experiences a high level of anxiety, the validity of the cognitive assessment is at stake, while anxiety impairs the efficiency of performances (19). The other way round, cognitive failures are positively correlated with stress and anxiety (20). Additionally, research of Santini et al. (21) indicates that the fear of pain during awake craniotomy correlates positively with the pain felt during the operation. Hence, someone who can calm down and motivate a patient during cognitive testing is highly important, not only for a patient's mood but also for the course of the operation. Additionally, someone who has the expertise to evaluate if patients´ failures during cognitive testing are the result of anxiety/ stress or refer to an underlying cognitive deficit is required. Moreover, results of our questionnaire show that patients are in need of someone who is there for them all the time. While those aspects are preferably combined in one person, coaching belongs in our opinion to the neuropsychologist.

Qualitative studies such as this can help clinicians to elaborate their role as a coach. However, coaching a patient during awake craniotomy remains personalized care. The stress and anxiety level of the patient, the way someone cope with frightening situations and a patient's personality are determinative.

References

1. Brown, P.D., Maurer, M.J., Rummans, T.A., Pollock, B.E., Ballman, K.V., Sloan, J.A., Boeve, B.F., Arusell, R.M., Clark, M,M,, Buckner J.C. (2005). A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: The impact of the extent of resection on quality of life and survival. *Neurosurgery, 57*, 495–504.
2. Duffau, H., Lopes, M., Arthuis, F., Bitar, A., Sichez, J-P., Van Effenterre, R., Capelle, L. (2005). Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*, 845–851.
3. Duffau, H. (2012) The challenge to remove diffuse low-grade gliomas while preserving brain functions. *Acta Neurochirurgica, 154,* 569-574.
4. Penleton, C., Zaidi, H.A., Chaichana, K.L., Raza, S.M., Carson, B.S., Cohen-Gadol, A.A., & Quinones-Hinojosa, A. (2012). Harvey Cushing's contributions to motor mapping: 1902-1912. *Cortex, 48* (1), 7-14.
5. Penfield, W., Rasmussen, T. (1950). The cerebral cortex of man: a clinical study of localization of function. Oxford: Macmillan.
6. Grossman, R., Ram, Z. (2013) Awake Craniotomy in Glioma Surgery, *European Association of NeuroOncology Magazine; 3 (Pre-Publishing Online)* http://www.kup.at/kup/pdf/11666.pdf
7. Duffau, H. (2010). Awake surgery for non-language mapping. *Neurosurgery, 66 (3)*, 523-529.
8. Szelényi, A., Bello, L., Duffau, H., Fava, E., Feigl, G.C., Galanda, M., Neuloh, G., Signorelli, F., & Sala, F. (2010). Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. *Neurosurgical Focus, 29 (2),* E7.
9. Wager, M., Du Boisgueheneuc, F., Pluchon, C., Bouyer, C., Stal, V., Bataille, B., Guillevin, C.M., Gil, R. (2013). Intraoperative monitoring of an aspect of executive functions: administration of the Stroop Test in 9 adult patients during awake surgery for resection of frontal glioma. *Neurosurgery, 72*, 169-181.
10. Danks, R.A., Rogers, M., Aglio, L.S., Gugino, L.D., & Black, P.M. (1998). Patient tolerance of craniotomy performed with the patient under local anesthesia and monitored conscious sedation. *Neurosurgery, 42*, 28-36.
11. Wrede, K.H., Stieglitz, L.H., Fiferna, A., Karts, M., Gerganov, V.M., Samii, M., von Gösseln, H.H., Lüdemann, W.O. (2011). Patient acceptance of awake craniotomy. *Clinical Neurology and Neurosurgery, 113*, 880-884.
12. Palese, A., Skrap, M., Fachin, M., Visioli, S., & Zannini, L. (2008). The experience of patients undergoing wake craniotomy. *Cancer Nursing, 31 (2)*, 168-172.
13. Khu, K.J., Doglietto, F., Radovanovic, I., Taleb, F., Mendelsohn, D., Zadeh, G., & Bernstein, M. (2010). Patients 'perceptions of awake and outpatient craniotomy for brain tumor: a qualitative study. *Journal of Neurosurgery, 112*, 1056-1060.
14. Whittle, I.R., Midgley, S., Georges, H., Pringle, A.M., & Taylor, R. (2005). Patient perceptions of "awake" brain tumour surgery. *Acta Neurochirurgica, 147*, 275-277.
15. Nossek, E., Matot, O., Shahar, T., Barzilai, O., Rapoport, Y., Gonen, T., Sela, G., Korn, A., Hayat, D., & Ram, Z. (2013). Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor. *Journal of Neurosurgery, 118*, 243-249.
16. Sime, A.M. (1976). Relationship of preoperative fear, type of coping, and information received about surgery to recovery from surgery. *Journal of Personality and Social Psychology, 34*, 716-724.

17. Henderson, A.S., Jorm, A.F., Korten, A.E., Jacomb, P., Christensen, H., & Rodgers, B. (1998). Symptoms of depression and axiety during adult life: evidence for a decline in prevalence with age. *Psychological Medicine, 28*, 1321-1328.
18. D'Angelo, C. Mirijello, A., Leggio, L., Ferrulli, A., Carotenuto, V., Icolaro, N., Miceli, A., D'Angelo, V., Gasbarrini, G., & Addolorato, G. (2008). State and trait anxiety and depression in patients with primary brain tumors before and after sugery: 1-year longitudinal study. *Journal of Neurosurgery, 108*, 281-286.
19. Derakshan, N., & Eysenck, M.W. (2009). Anxiety, processing efficiency and cognitive performance. *European Psychologist, 14 (2),* 168-176.
20. Mahoney, A.M., Dalby, J.T., & King, M. (1998). Cognitive failures and stress. *Psychological Reports, 82,* 1432-1434.
21. Santini, B., Talacchi, A., Casagrande, F., Casartelli, M., Savazzi, S., Procaccio, F., & Gerosa, M. (2012). Eligibility criteria and psychological profiles in patient candidates for awake craniotomy: a pilot study. *Neurosurgery and Anesthesiology, 24 (3),* 209-216.

CHAPTER 6

Effects of errorless and errorful face-name associative learning in moderate to severe dementia

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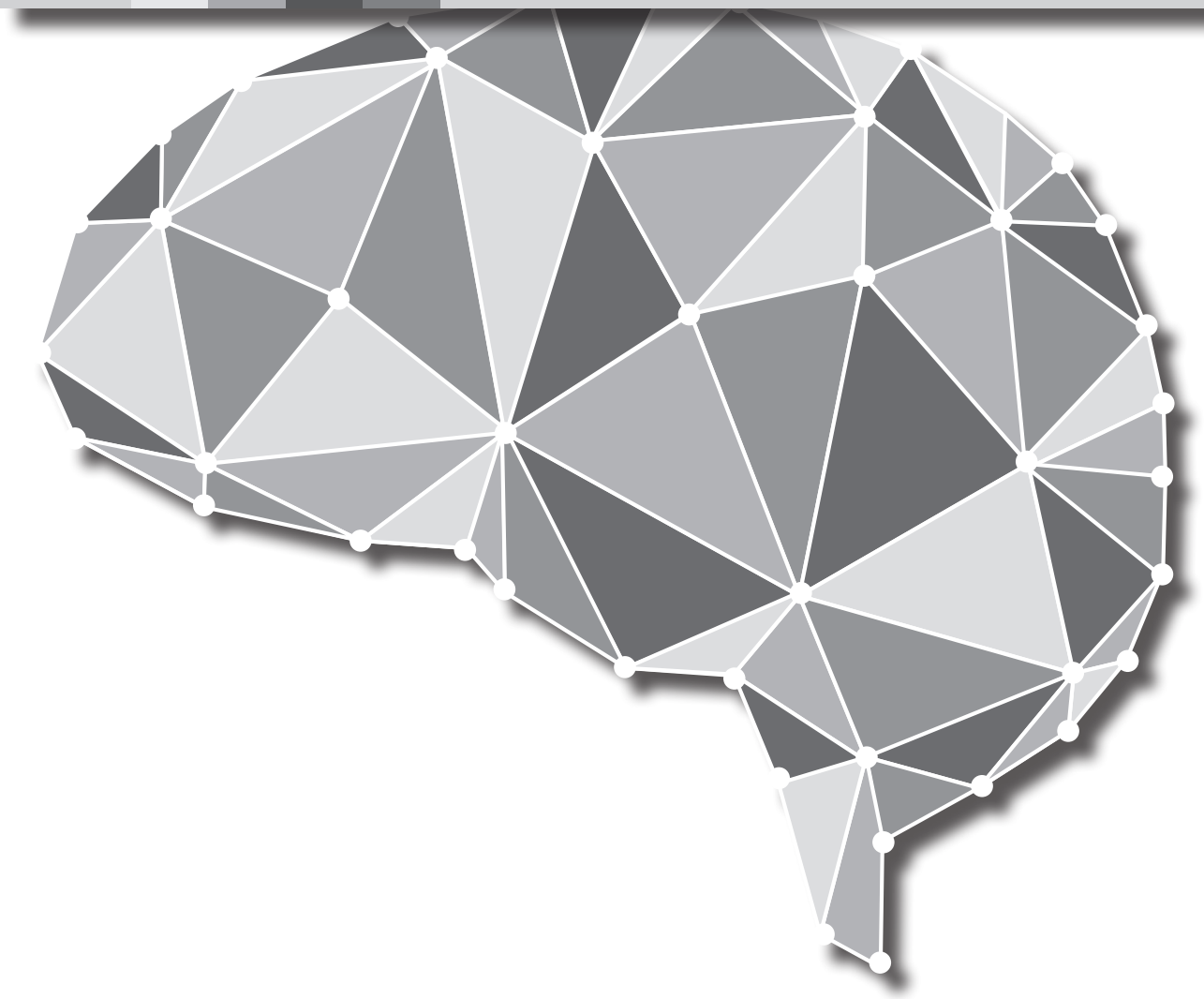
Aging Clinical and Experimental Research (2005), 17, 514-517



Abstract

The prevention of errors during learning has been found to be effective in overcoming memory problems in patients with amnesia compared with errorful or trial-and-error learning, possibly as a result of intact implicit memory function. Although errorless learning is a clinically promising technique used in cognitive training settings, to date only a few studies have examined errorless learning in patients with dementia.

The current study examined errorless and errorful learning using a face-name associative memory task in a group of moderate to severe dementia patients suffering from probable Alzheimer's disease (MMSE < 22; n = 10) using a fully counterbalanced within-subject design. Errorless learning had a significantly beneficial effect after two consecutive learning trials ($p = 0.01$). However, after an unfilled delay of 10 minutes, no significant differences in memory performance were found between errorless and errorful learning. Furthermore, current effects were much smaller compared with previous findings in healthy adults and early-stage dementia patients.

Although errorful learning resulted in better performance in a face-name associative memory task in patients with dementia, this effect was only short-lived. Thus, the beneficial effects of errorless learning are probably not due to intact implicit memory function, but may also be subserved by explicit memory, a memory system that is typically impaired in dementia. Also, the clinical applicability of errorless learning in teaching patients with moderate to severe dementia face-name associations is limited.

Introduction

Memory dysfunction is one of the most profound features of dementia. Other cognitive deficits that may occur are impairments in mental flexibility, attention, language, abstract reasoning, and problem solving (1). However, some cognitive functions are more likely to decline than others. For example, implicit memory, i.e., knowledge acquired in an "automatic" way without conscious recollection such as procedural learning, seems to be preserved longer than explicit memory, i.e., knowledge of which one is consciously aware, such as free recall of a word list (2).

Several cognitive training programs have used spared implicit memory function to overcome impairments in explicit memory in patients suffering from amnesia. One of the most fruitful methods involves the prevention of errors during learning. This concept was first introduced in a study in pigeons, which showed improved performance after learning without errors compared with trial-and-error learning (3). In humans, Baddeley and Wilson examined errorless learning in young participants, healthy older persons, and patients with memory impairments. Their mixed-etiology study group consisted of patients with severe amnesia due to neurological disease (e.g., stroke, Korsakoff's syndrome). A word-stem completion task was used in which word stems of two letters were presented. In the errorful condition, participants had to guess the correct word (hence inducing errors), after which the correct word was told by the experimenter. In the errorless condition, the correct word was given immediately by the experimenter. In both conditions, the words had to be remembered. The results showed a clear advantage of errorless learning, the effect being greatest in the patient group. The authors concluded that errorless learning is probably most effective in patients with severe explicit memory problems, in that errors produced during learning may be consolidated implicitly with no explicit correction, as in the case of participants with no memory impairments (4). A meta-analysis of the effects of memory rehabilitation techniques using intact implicit processing corroborated the positive effects of errorless learning in patients with memory impairments due to various neurological disorders, such as closed head injury, herpes simplex encephalitis and stroke, as well as in psychiatric patients with memory dysfunction, for example, schizophrenia and bipolar mood disorder. Overall, the effect size between errorless and errorful learning can be regarded as "large" ($d = 0.87$) (5).

To date, only a few studies have investigated the effects and clinical applicability of the errorless learning paradigm in patients with dementia. One case study used an errorless-learning approach in a patient suffering from Alzheimer's disease to learn face-name associations. A clear improvement was noted after four days of training. However, no errorful-learning condition was included, suggesting it is possible that improved performance may be the

result of task training itself rather than the errorless aspect (6). Another study investigated errorless learning in overcoming everyday memory problems in six patients suffering from Alzheimer's disease. Each patient received individual training tailored to specific memory problems the patient experienced in everyday life. For example, one patient worked on remembering the names of the people in the support group, and another wanted to remember events from her personal past. Results showed that an errorless-learning approach helped to improve memory performance on the individual tasks, although no control conditions were included (7). Lastly, the effect of errorless learning on the relearning of forgotten face-name associations was examined in a group of 12 patients with probable Alzheimer's disease in the early stage, i.e., with a Mini-Mental State Examination (MMSE) score over 18 (8). Here, a control condition was applied, in that memory for trained items was compared with memory for non-trained items. Results showed significantly improved memory performance after errorless learning compared with the control condition (9). However, no errorless-learning condition was included, making it difficult to claim that the effect was due to the prevention of errors during learning rather than to the general effect of training.

Although the results of the above studies on errorless learning in Alzheimer's dementia are promising, no studies have examined the learning of new face-name associations in moderate to severe Alzheimer's disease. This is of particular interest, since it has been suggested that errorless learning may be even more helpful in patients with little explicit memory function left. In turn, implicit knowledge about previously learned faces has been demonstrated in non-demented brain-damaged patients with prosopagnosia (10). Thus, the current study examines the effect of errorless learning in patients with moderate to severe dementia (MMSE < 22). The study design is within-subject and fully counterbalanced, using the same face-name associations for all participants in order to control for possible differences in familiarity. Also, it extends previous designs in studies on errorless learning in Alzheimer's dementia in that errorless learning is directly compared with an errorful condition, i.e. trial-and-error learning, to investigate the effects of errors occurring during the learning process.

Methods

Twenty residents of Stichting Stromenland, a psychogeriatric institution, were asked to participate in the research by means of a letter to a close relative, and their informed consent was obtained. All patients had been diagnosed with probable Alzheimer dementia in the moderate to severe stages, according to the criteria of the National Institute of

Neurological and Communicative Disorders and the Stroke/Alzheimer Disease and Related Disorders Association Criteria (11). In order to participate, patients had to be able to complete the MMSE. Eventually, 10 patients (5 male) were able to participate. The Dutch version of the National Adult Reading task (NLV) was used as an index of overall cognitive level (12,13). Education level was assessed and converted to years of education. Table 1 lists the characteristics of each participant.

Table 1 Characteristics of individual patients (gender, age, years of education, NLV- IQ and MMSE).

Patient	Gender	Age	Years of education	NLV-IQ	MMSE
1	M	81	6	76	9
2	F	85	6	66	10
3	M	73	10	104	22
4	M	89	10	81	16
5	M	84	6	94	18
6	M	82	6	90	17
7	F	80	6	70	13
8	F	86	6	85	20
9	F	81	6	71	18
10	F	77	10	88	17

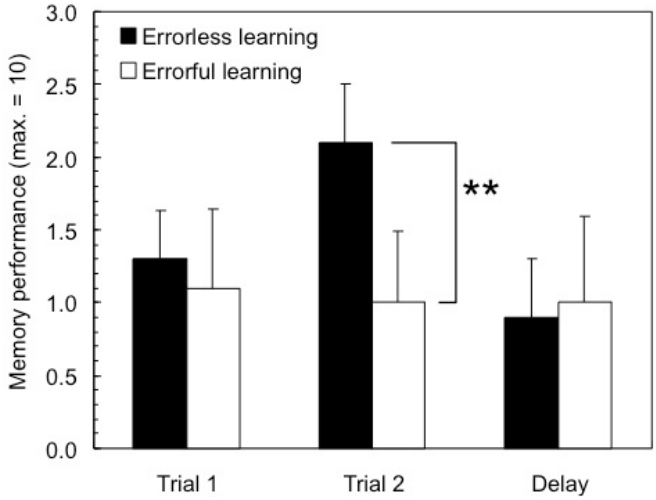
NLV = Dutch version of National Adult Reading Task; MMSE = Mini-Mental State Examination.

In the memory task, subjects were instructed to learn 10 face-name associations. The task consists of two conditions. In the errorful condition, subjects are prompted to guess the name associated with a face. After guessing the experimenter tells the subjects the correct name. Guessing results in erroneous responses, i.e., names that are incorrect. In the errorless condition, the experimenter provides the correct name for each face immediately. In this way, people are prevented from making errors. Two learning trials were followed by a test in which the faces were shown and subjects had to recall their names. A delayed test was also given ten minutes later (14). A within-subject design was applied, in which all subjects participated in each condition, with different face-name associations in both conditions. The time interval between the two conditions for each participant was one week. The order of the conditions was counterbalanced (i.e., half the participants started with errorless learning and half with errorful learning). The order of the individual trials was randomized for each participant.

Results

Figure 1 shows the memory performance of patients during errorless and errorful learning. A 2 × 3 repeated measures General Linear Model analysis with Condition (Errorless *vs* Errorful learning) and Trial (Test 1, 2 and Delay) as within-subject factors and Order of condition (Errorless first or Errorful first) as between-subject factor was carried out. The main effects of Trial ($F(2,7) = 3.47$) and Condition ($F(1,8) = 1.45$) were not significant, but a significant Trial × Condition interaction effect was found ($F(2,7) = 6{,}02$, $p = 0.03$). The order in which the conditions were performed did not result in overall differences in performance ($F(1,8) = 2.25$) and did not interact with any of the other variables (all $Fs < 0.53$). Post-hoc paired-samples *t*-tests were carried out to further examine this interaction, and a significant difference between errorless and errorful learning was found on Trial 2 ($t(9) = 3.50$, $p = 0.007$), with better performance in the errorless learning condition.

Figure 1 Number of correct face-name associations after errorless and errorful learning. Trial 1 reflects memory performance after first presentation of face-name associations, Trial 2 memory performance after second presentation. Delay is memory performance after ten minutes (** p = 0.007).



Discussion

This study investigated the effects of errorless and errorful learning in moderate to severe Alzheimer's dementia. The results of this study show that errorless learning results in better memory performance, but that repeated presentation is required. This is in line with evidence showing that a combination of an errorless learning paradigm and repeated

presentation is very effective (15). In addition, no long-term effect of errorless learning was found, probably the result of accelerated memory decay or "rapid forgetting", which is commonly reported in patients suffering from Alzheimer's disease (16). Thus, although errorless learning resulted in better face-name memory performance after two learning trials, the overall effect of errorless learning in moderate to severe dementia appears to be small. The current results hence do not support the suggestion of Baddeley and Wilson that the beneficial effect of errorless learning is probably the largest in people with severe memory problems (4).

With respect to the clinical application of errorless learning, the usefulness of the errorless learning technique on memory for new face-name associations in moderate to severe dementia seems limited. However, a thorough review of memory interventions in dementia has listed errorless learning among the most effective memory techniques that can be applied in clinical settings (17). The strength of errorless learning lies in the fact that this approach enables the development of individually tailored interventions aimed at memory problems which patients and their relatives report to be hampering everyday functioning. The current study obviously used general information, with little relevance to the specific memory problems of individual patients. Furthermore, poor performance on the task as a whole possibly indicated that the memory impairments of the current patient group were too severe, in that their implicit learning capacity may also have been impaired. In turn, perhaps the effects of errorless learning are simply not due to intact implicit learning capabilities. For example, Hunkin et al. have examined the relation between implicit memory measures, i.e., priming, and the effect of errorless learning. Here, no correlation between implicit memory measures and errorless performance was found (18). This finding led the authors to conclude that the prevention of errors results in better explicit memory performance, which may be due to partly intact explicit learning processes. In line with this suggestion, a recent study using the same face-name associative learning paradigm as in the present study in healthy younger and older adults showed that especially the younger participants benefited from errorless learning (14). Moreover, a large study comparing young and older adults on errorless learning of spatial locations compared with trial-and-error learning was set up to assess the contribution of implicit and explicit memory processes to the effects of errorless learning. Results also showed the clear advantage of errorless learning in younger participants, but not in the older group. Also, the effect of errorless learning appeared to be clearly related to explicit memory function (19). However, the present study was not designed to address this question directly. Clearly, further research is needed to examine the underlying cognitive processes of errorless learning benefits.

In sum, this is the first study comparing errorless and errorful learning of face-name associations in patients with Alzheimer's dementia. Results show that people with moderate to severe Alzheimer's dementia had better memory performance after errorless learning in comparison with errorful learning on a face-name association memory task, although this effect was not very long lasting. Also, the beneficial effects of errorless learning were smaller in the present group, compared with the effects in previous studies on healthy adults and early-stage dementia patients. This suggests that it is probably not only intact implicit memory that is responsible for the effects of errorless learning.

Acknowledgments

The authors would like to thank Stichting Stromenland for their cooperation in this research. Roy Kessels was supported by a VENI research grant (#451-02-037) from the Netherlands Organization for Scientific Research (NWO).

References

1. Knopman, D., & Selnes, O. (2003). Neuropsychology of dementia. In: Heilman, K.M., & Valenstein, E., eds. *Clinical neuropsychology, 4th Ed*. Oxford, UK: Oxford University Press.
2. Kuzis, G., Sabe, L., Tiberti, C., Merello, M., Leiguarda, R., & Starkstein, S.E. (1999). Explicit and implicit learning in patients with Alzheimer disease and Parkinson disease with dementia. *Neuropsychiatry Neuropsycholy and Behavioral Neurology, 12*, 265-269.
3. Terrace, H.S. (1963). Discrimination learning with and without "errors". *Journal of the Experimental Analysis of Behavior, 6*, 1-27.
4. Baddeley, A., & Wilson, B.A. (1994). When implicit learning fails: amnesia and the problem of error elimination. *Neuropsychologia, 32*, 53-68.
5. Kessels, R.P.C., & de Haan, E.H.F. (2003). Implicit learning in memory rehabilitation: a meta-analysis on errorless learning and vanishing cues method. *Journal of Clinical and Experimental Neuropsychology, 25*, 805-814.
6. Winter, J., & Hunkin, N.M. (1999). Re-learning in Alzheimer's Disease. *International Journal of Geriatric Psychiatry, 14,* 983-990.
7. Clare, L., Wilson, B.A., Carter, G., Breen, K., Gosses, A., & Hodges, J.R. (2000). Intervening with everyday memory problems in dementia of Alzheimer type: an errorless learning approach. *Journal of Clinical and Experimental Neuropsychology, 22,* 132-146.
8. Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189-198.
9. Clare, L., Wilson, B.A., Carter, G., Roth, I., & Hodges, J.R. (2002). Relearning face-name associations in early Alzheimer's disease. *Neuropsychology, 16*, 538-547.
10. Tranel, D., & Damasio, A.R. (1985). Knowledge without awareness: an autonomic index of facial recognition by prosopagnosics. *Science, 228*, 1453-1454.
11. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M. (1984). Clinical Diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*, 939-944
12. Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). De Nederlandse Leestest voor Volwassenen: een maat voor het premorbide intelligentieniveau. [The Dutch Adult Reading Test: a measure of premorbid intelligence]. *Tijdschrift voor Gerontologie en Geriatrie, 22*, 15-19.
13. Taylor, R. (2000). National Adult Reading Test performance in established dementia. *Archives of Gerontology and Geriatrics, 29*, 291-296.
14. Kessels, R.P.C., & de Haan, E.H.F. (2003). Mnemonic strategies in older people: A comparison of errorless and errorful learning. *Age and Ageing, 32*, 529-533.
15. Clare, L., Wilson, B.A., Carter, G., & Hodges, J.R. (2003). Cognitive rehabilitation as a component of early intervention in Alzheimer's disease: a single case study. *Aging & Mental Health, 7*, 15-21.
16. Vanderploeg, R.D., Yuspeh, R.L., & Schinka, J.A. (2001). Differential episodic and semantic memory performance in Alzheimer's disease and vascular dementias. *Journal of the International Neuropsychological Society, 7*, 563-573.
17. Grandmaison, E., & Simard, M. (2003). A critical review of memory stimulating programs in Alzheimer's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences, 15*, 130-144.

18. Hunkin, N.M., Squires, E.J., Parkin, A.J., & Tidy, J.A. (1998). Are the benefits of errorless learning dependent on implicit memory? *Neuropsychologia, 36*, 25-36.
19. Kessels, R.P.C., Te Boekhorst, S., & Postma, A. (2005). The contribution of implicit and explicit memory to the effects of errorless learning: a comparison between young and older adults. *Journal of the International Neuropsychological Society, 11*, 144-151.

CHAPTER 7

Cognition in the early stage of type 2 diabetes

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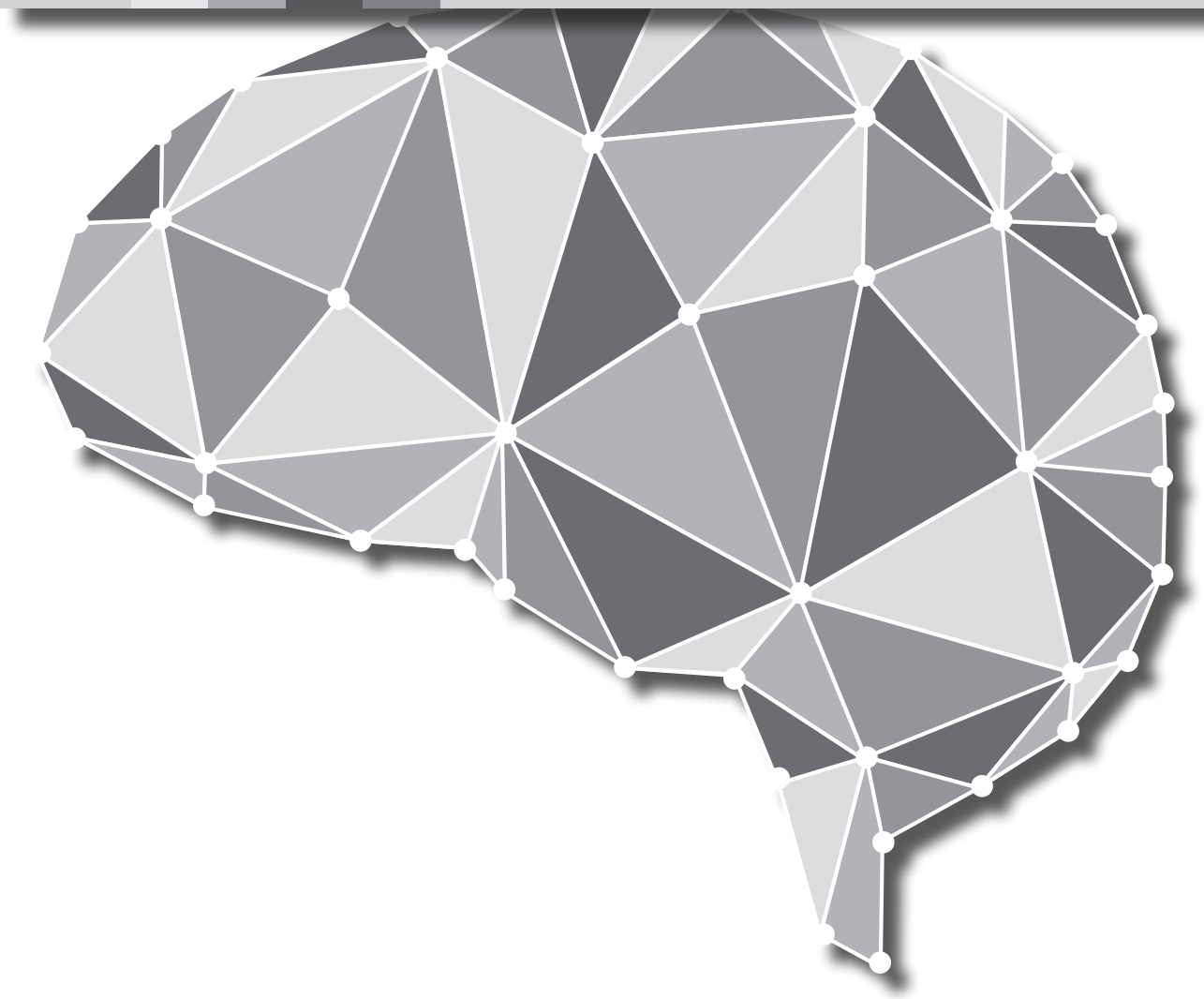
Diabetes Care (2009), 32, 1261-1265



Abstract

Type 2 diabetes is known to be associated with decrements in memory and executive functions, and information-processing speed. It is less clear, however, at which stage of diabetes these cognitive decrements develop and how they progress over time. In this study, we investigated cognitive functioning of patients with recently screen-detected type 2 diabetes, thus providing insight in the nature and severity of cognitive decrements in the early stage of the disease. Possible risk factors were also addressed.

Included in this study were 183 diabetic patients from a previously established study cohort and 69 control subjects. A full neuropsychological assessment, addressing six cognitive domains, was made for each participant. Raw test scores were standardized into *z* scores per domain and compared between the groups. Possible risk factors for cognitive decrements were examined with multivariate linear regression.

Relative to scores for the control group, mean *z* scores were between 0.01 and 0.2 lower in the diabetic group across all domains, but after adjustment for differences in IQ between patients and control subjects only memory performance was significantly reduced (mean difference -0.15 (95% CI -0.28/-0.03). A history of macrovascular disease and current smoking were significant determinants of slower information-processing speed in patients with diabetes.

This study shows that modest cognitive decrements are already present at the early stage of type 2 diabetes. A history of macrovascular disease and smoking are significant risk factors for some early decrements.

Introduction

Type 2 diabetes is associated with accelerated cognitive decline (1) and an increased risk of dementia (2,3), particularly in older individuals. Previous studies have shown decrements in memory function, executive function, and information-processing speed (4,5). These decrements in cognitive functioning are associated with modest brain atrophy and vascular lesions on brain magnetic resonance imaging (6). Diabetes-related factors, such as insulin resistance, chronic hyperglycemia, hypertension, and lipid disorders probably are relevant determinants (7,8).

It is unclear in which stage of diabetes the cognitive decrements become manifest and how they progress over time. Most studies have focussed on patients with a known history of diabetes of several years (9). However, type 2 diabetes typically develops insidiously and may often be undiagnosed in the early stages. Therefore, cognitive decrements may start to develop years before the actual diagnosis, even in the pre-diabetes stages. Detailed neuropsychological data on the early stage of type 2 diabetes are not yet available. Moreover, possible risk factors for early cognitive decrements are incompletely known.

In this study we assessed cognition in the early stage of diabetes by means of a detailed neuropsychological assessment (NPA) in a substantial population of patients with recently screen-detected diabetes. Possible risk factors were also addressed.

Research design and methods

The ADDITION study

The Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION) study is a multinational randomized trial involving 3057 screen-detected type 2 diabetes patients that compares the effectiveness of an intensified multifactoral treatment with usual care on 5-year cardiovascular morbidity and mortality rates in a primary care setting (10).

In the Netherlands, 56.987 individuals without known diabetes were offered a questionnaire, and those with a score above threshold underwent further glucose testing. Eventually, 586 participants had a diagnosis of type 2 diabetes according World Health Organization 1999 criteria (11) and 498 people were included in the study. Inclusion started in 2002 and ended in 2004.

In the ADDITION study, usual care is performed according to the different national guidelines from the three countries (in the Netherlands, the guidelines are from the Dutch College of General Practitioners [12]). The intensified multifactorial treatment consists of lifestyle advice regarding diet, physical activity, and smoking; protocol-driven strict regulation of blood glucose (A1c ≤6.5-7.0%), blood lipids (cholesterol <3.5 mmol/l), and blood pressure (<130/80 mmHg) and in those with blood pressure >120/80 mmHg prescription of acetyl salicylic acid and an ACE inhibitor. The primary outcome measure of the study is the combination of cardiovascular morbidity and mortality, all revascularisations, or non-traumatic amputations, whichever came first.

Inclusion in the Cognition part of the ADDITION study
Cognition was assessed in an add-on project to the main ADDITION study in the Netherlands. Patients were invited to participate by an information letter from the study group and their family physician. Control subjects were peers from the patients, and both groups were matched for age, sex, and level of education. All patients and control subjects gave informed consent. Time between initial screening and inclusion in the Cognition part of the ADDITION study was 3-4 years.

Inclusion criteria
Inclusion and exclusion criteria for the present study were identical to those of the ADDITION study. All participants were 50-70 years at time of screening (2002-2004). Within 6 weeks after diagnosis of type 2 diabetes, treatment started. Randomization was performed at practice level, so people were treated according to the group (intensified treatment/usual care) their family physician had been randomized assigned to.

NPA was performed 3,6 ± 0,56 (mean ± SD) years after the screening date. Patients were excluded from the ADDITION trial if they were known to have a history of alcohol or drug abuse, psychosis, personality disorder, dementia, or emotional, psychological, or neurological disorder, unrelated to diabetes, that was likely to invalidate informed consent or limit their ability to comply with the protocol requirements. For both the ADDITION trial and the Cognition part, individuals with a previous noninvalidating stroke could participate. At the time of screening, participants with or treated for malignant disease or other disease that limited life expectance <5 years were excluded. Control subjects had a fasting blood glucose <7.0 mmol/l, according to American Diabetes Association criteria (13).

NPA

The NPA was performed with a previously established test battery consisting of 12 verbal and nonverbal tasks addressing six cognitive domains (abstract reasoning, memory function, information-processing speed, attention and executive function, and visuoconstruction) as described previously (14). For the present study, the domain language comprehension was added and assessed with the Token Test (short form) (15). The domain memory was divided into four subdomains: working memory, immediate memory and learning rate, forgetting rate and incidental memory (the amount of information that can be memorized if one was not explicitly asked to remember something) (14). IQ was measured by the Dutch version of the National Adult Reading Test (NART) (16). This test is constructed to estimate premorbid levels of intelligence and is relatively independent of brain damage acquired after adulthood (16). A depression scale (Community Mental Health Assessment; 17) was used to assess the potential effect of mood disturbances on cognition. Scores ≥16 were labelled as depressive symptoms.

The physical examination and administration of the neuropsychological tests were performed at the patients' homes. The tests were administrated in a fixed order, and the entire battery took about 90 minutes to complete.

Participant characteristics and risk factor assessment

Demographic variables and possible risk factors were recorded in a standardized interview. Educational level was recorded using seven categories (*1*, <6 years of education; *2*, 6 years; *3*, 8 years; *4*, 9 years; *5*, 10-11 years; *6*, 12-18 years; *7*, >18 years of education) . Height and weight were measured and BMI was calculated as weight in kilograms divided by the square of height in meters. Smoking was classified as current, past or never. Alcohol consumption was recorded using six categories (*0*, no alcohol at all; *1*, up to three units/week; *2*, 4-10 units/week; *3*, 11-20 units/week; *4*, 21-30 units/week; *5*, > 30 units/week). Participants in category 5 were excluded. A1c (percent) and cholesterol level (millimoles per liter) were measured in the week of the NPA and analysed at the regional hospital. Systolic and diastolic blood pressures (millimetres of mercury) were measured at the beginning and the end of the neuropsychological assessment; measurements were averaged. Hypertension was defined as a mean systolic blood pressure >160 mmHg, a mean diastolic blood pressure >95 mmHg, or use of blood pressure-lowering medication. These relatively high cutoff values were used because otherwise >90% of the patients would be classified as hypertensive, which would hamper the assessment of the role of this risk factor in the regression analyses. Macrovascular disease was defined as history of myocardial infarction, stroke, or surgery or endovascular treatment for carotid, coronary, or peripheral arterial disease.

Analysis

The differences between patients and control subjects were examined with Student's *t* test for means, Mann-Whitney *U* tests for non-parametric data, and chi-square test for proportions. To analyse the difference in cognitive functioning between diabetes patients and control subjects, raw test scores of the NPA of both groups were standardized into *z* scores per domain. Mean *z* scores of the six cognitive domains were compared between the groups with univariate ANOVAs. Estimated mean differences between group differences were calculated and are presented with 95% CIs. Because the estimated premorbid IQ was significantly different between diabetes patients and control subjects, the NART-IQ was used as a covariate. To further assess the potential confounding effect of the NART-IQ imbalance, we performed a secondary analysis including all the controls (n=69) and an exact age-, sex-, and NART-IQ- frequency matched selection of the patients (n=143).

The relation between metabolic and vascular risk factors and cognition within the type 2 diabetes patients was assessed with linear regression analyses (adjusted for sex, age, and NART-IQ). To limit the number of analyses, only the domains of information-processing speed and memory were entered in these regression analyses, because these domains are known to be particularly sensitive to the effects of type 2 diabetes (9).

Results

Participant characteristics

A total of 183 patients with diabetes and 69 control subjects were included in the Cognition part of the ADDITION study. Patients and control subjects were balanced on sex, age, and educational level (Table 1). However, control subjects had a significantly higher estimated premorbid IQ.

There were differences in the metabolic and vascular profile between patients and control subjects (Table 1). Control subjects had a significant lower BMI, and they consumed significantly more units alcohol per week than the patient group.

Vascular risk factors in patients in both treatment groups were well controlled. Those who received multifactoral treatment had a slightly lower A1c level (mean ± SD difference -0.23 ± 0.07%), cholesterol (mean difference -0.53 ± 0.14 mmol/l) and mean arterial pressure (mean difference -3.05 ± 1.78 mmHg) than those who received usual care.

Table 1 Participant characteristics.

	Patients with type 2 diabetes	Control subjects
n	183	69
Sex (% males)	61,2	47,8
Mean age (years)	63,0 ± 5,4	62,7 ± 6,4
Education level (1-7)	4 (4-5)	5 (4-6)
Estimated premorbid IQ	96,7 ± 19,6	103,8 ± 16,3**
BMI (kg/m^2)	30,4 ± 5,3	27,4 ± 4,2 **
Current smoking (%)	21,2	11,8
Alcohol (0-5)	1 (0-2)	2 (1-3) *
Depressive symptoms (%)	9,8	5,8
A1c (%)	6,2 ± 0,5	5,5 ± 0,3 **
Cholesterol (mmol/l)	4,1 ± 1,0	5,7 ± 1,0 **
Use lipid-lowering medication (%)	78,7	15,9 **
Systolic blood pressure (mmHg)	143 ± 20	140 ± 21
Diastolic blood pressure (mmHg)	82 ± 10	81 ± 12
Hypertension (%)	85,2	36,2**
Use antihypertensive drugs (%)	81,4	23,2**
Macrovascular disease (%)	14,8	4,3**

Data are means ± SD, proportion (in percent), and median (interquartile range), unless indicated otherwise.
* : p<.05 ** : p<.01

Cognitive functioning

The diabetes group performed significantly worse on memory functions, information-processing speed, attention and executive functions and language comprehension in the unadjusted analyses, but the mean differences between the groups were small (-0.21 to -0.35) (Table 2). After adjustment for NART-IQ, only memory functions differed significantly between the groups (-0.15). The memory subdomains 'immediate memory and learning rate' and 'incidental memory' differed significantly between the groups after adjustment for NART- IQ. The results of the secondary analyses, in a selected subpopulation with exact matching for age, sex, and NART-IQ, showed an identical cognitive profile with similar effect sizes (results not shown). There were no significant differences in cognitive functioning between the patients who received multifactor treatment compared with patients who received usual care (results not shown) .

Table 2 Estimated Mean Differences (95% CI).

	Unadjusted	Adjusted for NART-IQ
Abstract reasoning	-0.20 (-0.48 to 0.08)	-0.01 (-0.26 to 0.23)
Memory	-0.21 (-0.32 to -0.08)*	-0.15 (-0.28 to -0.03)*
working memory	-0.20 (-0.42 to 0.01)	-0.07 (-0.27 to 0.13)
immediate memory & learning rate	-0.24 (-0.41 to -0.06)**	-0.18 (-.035 to -0.003)*
forgetting rate	0.04 (-0.18 to 0.26)	0.04 (-0.18 to 0.26)
incidental memory	-0.49 (-0.73 to -0.17)**	-0.42 (-0.71 to -0.14)**
Information processing speed	-0.26 (-0.48 to -0.03)*	-0.13 (-0.33 to 0.08)
Attention and executive functions	-0.23 (-0.42 to -0.04)*	-0.12 (-0.29 to 0.05)
Visuoconstruction	-0.23 (-0.52 to 0.05)	-0.10 (-0.37 to 0.17)
Language comprehension	-0.35 (-0.65 to -0.04)*	-0.19 (-0.49 to 0.11)

*: p<.05 **: p<.01

Table 3 Determinants of performance on memory and information processing speed, adjusted for sex, age, and NART-IQ (regression analyses).

	Patients with diabetes type 2					
	Memory			**Information Processing Speed**		
	B		β	**B**		β
Age	-0.02	(-0.04 to -0.01)**	-0.26	-0.07	(-0.08 to -0.05)**	-0.44
Sex	-0.03	(-0.16 to 0.10)	-0.03	-0.07	(-0.27 to 0.12)	-0.04
BMI	0.003	(-0.01 to 0.02)	0.03	-0.02	(-0.04 to 0.001)	-0.11
Current smoking	-0.04	(-0.20 to 0.12)	-0.03	-0.26	(-0.50 to -0.03)*	-0.13
A1c	0.004	(-0.13 to 0.14)	0.004	0.004	(-0.20 to 0.20)	0.002
Cholesterol	0.02	(-0.05 to 0.09)	0.04	-0.07	(-0.17 to 0.03)	-0.08
Hypertension	0.06	(-0.13 to 0.24)	0.04	-0.17	(-0.47 to 0.10)	-0.08
Systolic blood pressure (per 10 mmHg)	0.001	(-0.03 to 0.04)	0.01	0.02	(-0.04 to 0.07)	0.04
Diastolic blood pressure (per 10 mmHg)	-0.04	(-0.10 to 0.03)	-0.08	-0.04	(-0.13 to 0.05)	-0.05
Macrovascular disease	-0.13	(-0.28 to 0.02)	-0.12	-0.30	(-0.51 to -0.09)**	-0.17
Depressive symptoms	-0.08	(-0.31 to 0.14)	-0.05	0.01	(-0.34 to 0.35)	0.002

* : p<.05 ** : p<.01
Data are presented as regression coefficient *B* (95% Confidence Interval) and standardized β.

Possible risk factors

Age was inversely related with performance on tasks for memory and information-processing speed in diabetic patients (Table 3). Neither sex, nor HbA1 levels, blood pressure, cholesterol levels, or BMI was significantly related to cognitive performance. A history of macrovascular disease, however, was associated with reduced information-processing speed. Current smoking also had a significant effect on the reduced information-processing speed. Depressive symptoms were not significantly related to memory functions or information-processing speed. In control subjects, only age was inversely related with performances on memory and information-processing tasks (not shown in table).

Conclusions

This study shows that patients with recently screen-detected type 2 diabetes performed significantly worse on memory functions, in particular, the immediate and the incidental memory, compared with control subjects. A history of macrovascular diseases and current smoking were the strongest determinants of a lower information processing speed in the diabetic group.

The effect sizes for the difference in cognition between the diabetic and control group found in this study are small compared with those in other studies (9), possibly reflecting the relatively short duration of diabetes in our population. Indeed, in a previous study with the same NPA battery, we found effect sizes of 0.3-0.4 among patients with mean diabetes duration of eight years (8). Another study using the same assessment battery in patients with a diabetes duration of 5-9 years showed effect sizes of 0.2-0.3 (18). Diabetes duration thus seems to be linked to the effect sizes of the studies: the longer the known diabetes duration, the bigger the effect size. In the present study we observed a small difference in language comprehension between patients and control subjects that was not significant after adjustment for NART-IQ. The meaning of this finding is not clear. The domain language comprehension is seldom addressed in studies on cognition in patients with type 2 diabetes. Moderate correlations between the token test and measures of short-term memory have been reported in a previous study on non-diabetic subjects (19), however, our results do not indicate that our patients performed worse on measures of short term memory (working memory). The observed small effect on this test is well outside the range of what would be considered as abnormal performance and is therefore unlikely to confound performance on the other cognitive tests.

Further research is necessary to see how the cognitive decrement in our patients will develop over time and whether they also will develop problems in executive functions and information-processing speed as described in other studies. The patients included in this study will be followed over time and a second NPA will be performed in a few years.

The relation between macrovascular diseases, smoking, and cognition has also been found in previous studies of patients with diabetes (8,20). Traditionally, hypertension is also thought to mediate the association between diabetes and cognitive dysfunction (4,21), but results of previous, mostly cross-sectional, studies do not consistently show this relation, in line with our findings. Also in nondiabetic subjects, the association between hypertension and cognitive functioning varies with age and time of exposure and is most evident when blood pressure is assessed in midlife and cognition in late life (22). Therefore, the association may be less evident in a cross-sectional study in a relatively older population, such as ours.

Regarding glycemic control, the literature mostly shows a negative relation between HbA1c (chronic exposure to hyperglycemia) and cognition in type 1 (23), and type 2 diabetes (24, 25). We could not confirm this relationship. It is possible that we did not find this relationship because of the relatively strict metabolic control in our patients, but it is also possible that the negative effect of A1c on cognition becomes more evident after longer diabetes duration.

Strength of our study is the measurement of cognitive functions in the early stage of the disease. Previous studies focussed mainly on patients with longer diabetes duration. This study gives more information on early cognitive decrements and shows, in combination with other studies that used the same NPA in patients with a longer duration of diabetes, that the decrements seem to be progressive over time.

A limitation of our study is the difference in IQ scores of patients and control subjects. Control subjects had significantly higher IQ scores compared with those for the diabetic patients. We therefore had to adjust the analyses for NART-IQ. In a secondary analysis with exact matching for age, sex and NART-IQ, patients still performed poorer on memory functions than control subjects. Besides a difference in IQ scores, there also was a nonsignificant higher proportion of males in the patient group, but sex was unrelated to performances in any cognitive domain (Table 3).

Another limitation is the time between screening and the NPA, which is between three and four years. Although this period is relatively short, we cannot say anything about the cognitive functioning in the first stage of type 2 diabetes. On the other hand, because of the

screening procedure, the diabetic patients in our study are likely to have had their diabetes diagnosed some years earlier; thus they may be in the same period of their disease as patients in usual care with a recent diagnosis of type 2 diabetes.

Because of the delay between screening and the NPA, half of the diabetes patients had received multifactoral-intensified treatment for a period of 3-4 years. Although levels of A1c, cholesterol, and blood pressure were indeed better in the intensively treated group, both groups showed good control on these risk factors, and no effect of treatment allocation on cognition was observed in the present interim analysis. It is possible that a longer treatment duration or contrast in risk factor levels between the groups is required to observe effects on cognition. This possibility will be addressed in the follow-up study, once the treatment period has been completed.

In summary, cognitive decrements can be found in the early stages of type 2 diabetes. This finding may have implications for diabetes education and self-management behavior in diabetic patients. Diabetes educators should at least take into account the immediate memory and learning rate and the incidental memory of patients with a recent diagnosis of diabetes. If one wishes to prevent diabetes-associated cognitive decrements interventions may need to be initiated at a very early stage. Offering a smoking cessation consultation would be the best option in those patients who are smokers. Whether other therapies might be beneficial to decrease the risk on cognitive impairment remains uncertain.

Acknowledgements

The ADDITION study in the Netherlands was funded by grants from Novo Nordisk Netherlands, GlaxoSmithKline Netherlands, and Merck Netherlands.

References

1. Cukierman, T., Gerstein, H.C., & Williamson, J.D. (2005). Cognitive decline and dementia in diabetes – systematic overview of prospective observational studies. *Diabetologia, 48* (12), 2460-2469.
2. Arvanitakis, Z., Wilson, R.S., Bienias, J.L., Evans, D.A., & Bennett, D.A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology, 61*, 661-666.
3. Ott, A., Stolk, R.P., van Harskamp, F., Pols, H.A.P., Hofman, A., & Breteler, M.M.B. (1999). Diabetes mellitus and the risk of dementia. *Neurology, 53*, 1937-1942.
4. Stewart, R., & Liolitsa, D. (1999). Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabetic Medicine, 16*, 93-112.
5. van den Berg, E., Kessels, R.P.C., Kappelle, L.J., de Haan, E.H.F., & Biessels, G.J. (2006). Type 2 diabetes, cognitive function and dementia: vascular and metabolic determinants. *Drugs of Today, 42*, 741-754.
6. Manschot, S.M., Brands, A.M.A., van der Grond, J., Kessels, R.P.C., Algra, A., Kappelle, L.J., & Biessels, G.J. (2006). Brain Magnetic Resonance Imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes, 55* (4), 1106-1113.
7. Biessels, G.J., Staekenburg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurology, 5* (1), 64-74.
8. Manschot, S.M., Biessels, G.J., de Valk, H., Algra, A., Rutten, G.E.H.M., van der Grond, J., & Kappelle L.J. (2007). Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia, 50*, 2388-2397.
9. Awad, N., Gagnon, M., & Messier, C. (2004). The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *Journal of Clinical and Experimental Neuropsychology, 26*, 1044-1080.
10. Sandbaek, A., Griffin, S.J., Rutten, G., Davies, M., Stolk, R., Khunti, K., Borch-Johnsen, K., Wareham, N.J., & Lauritzen, T. (2008). Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia, 51*, 1127-1134.
11. Alberti, K.G.M.M., & Zimmet, P.Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic Medicine, 15*, 539-553.
12. Rutten, G.E.H.M., De Grauw, W.J.C., Nijpels, G., Goudswaard, A.N., Uitdewaal, P.J.M., Van der Does, F.E.E., Heine, R.J., Van Ballegooie, E., Verduijn, M.M., & Bouma, M. (2006). NHG-Standaard Diabetes Mellitus type 2. *Huisarts & Wetenschap, 49* (3), 137-152.
13. American Diabetes Association (1997). Standards of medical care for patients with diabetes mellitus. *Diabetes Care, 20*, S5-S13.
14. Brands, A.M.A., Kessels, R.P.C., Hoogma, R.P.L.M., Henselmans, J.M.L., van der Beek Boter, J.W., Kappelle, L.J., de Haan, E.H.F., & Biessels, G.J. (2006). Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. *Diabetes, 55*, 1800-1806.
15. Graetz, P., de Bleser, R., & Willmes, K. (1992). *Akense Afasie Test*. Lisse, The Netherlands: Swets & Zeitlinger.
16. Schmand, B., Lindeboom, J., & van Harskamp, F. (1992). *Nederlandse Leestest voor Volwassenen [Dutch Adult Reading Test]*. Lisse, The Netherlands: Swets & Zeitlinger.

17. Bouma, J., Ranchor, A.V., Sanderman, R., & van Sonderen, E. (1995). *Het meten van symptomen van depressie met de CES-D: een handleiding.* Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.
18. van den Berg, E., Dekker, J., Nijpels, G., Kessels, R.P.C., Kappelle, L.J., de Haan, E.H.F., Heine, R.J., Stehouwer, C.D.A., & Biessels, G.J. (2008). Cognitive functioning in elderly perons with type 2 diabetes and metabolic syndrome: the Hoorn study. *Dementia and Geriatric Cognitive Disorders, 26*, 261-269.
19. Lesser, R. (1976). Verbal and non-verbal memory components in the Token Test. *Neuropsychologia*, *14*, 79-85.
20. Arvanitakis, Z., Wilson, R.S., Li, Y., Aggerwal, N.T., & Bennett, D.A. (2006). Diabetes and function in different cognitive systems in older individuals without dementia. *Diabetes Care*, *29*, 560-565.
21. Hassing, L.B., Hofer, S.M., Nilsson, S.E., Berg, S., Pedersen, N.L., McClearn, G., & Johansson, B. (2004). Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age and Ageing*, *33*, 355-361.
22. Kloppenborg, R.P., van den Berg, E., Kappelle, L.J., & Biessels, G.J. (2008). Diabetes and other vascular factors for dementia: which factor matters most? A systematic review. *European Journal of Pharmacology*, *585*, 97-108.
23. Brands, A.M.A., Biessels, G.J., de Haan, E.H.F., Kappelle, L.J., & Kessels, R.P.C. (2005). The effects of type 1 diabetes on cognitive performance. *Diabetes Care*, *29*, 726-735.
24. van Harten, B., Oosterman, J., Muslimovic, D., van Loon, B.J.P., Scheltens, P., & Weinstein, H.C. (2007). Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes. *Age and Ageing,* 36, 164-170.
25. Munshi, M., Grande, L., Hayes, M., Ayres, D., Suhl, E., Capelson, R., Lin, S., Milberg, W., & Weinger, K. (2006). Cognitive dysfunction is associated with poor diabetes control in older adults. *Diabetes Care*, *29*, 1794-1799.

CHAPTER 8

The Telephone Interview for Cognitive Status (Modified): relation with a comprehensive neuropsychological assessment

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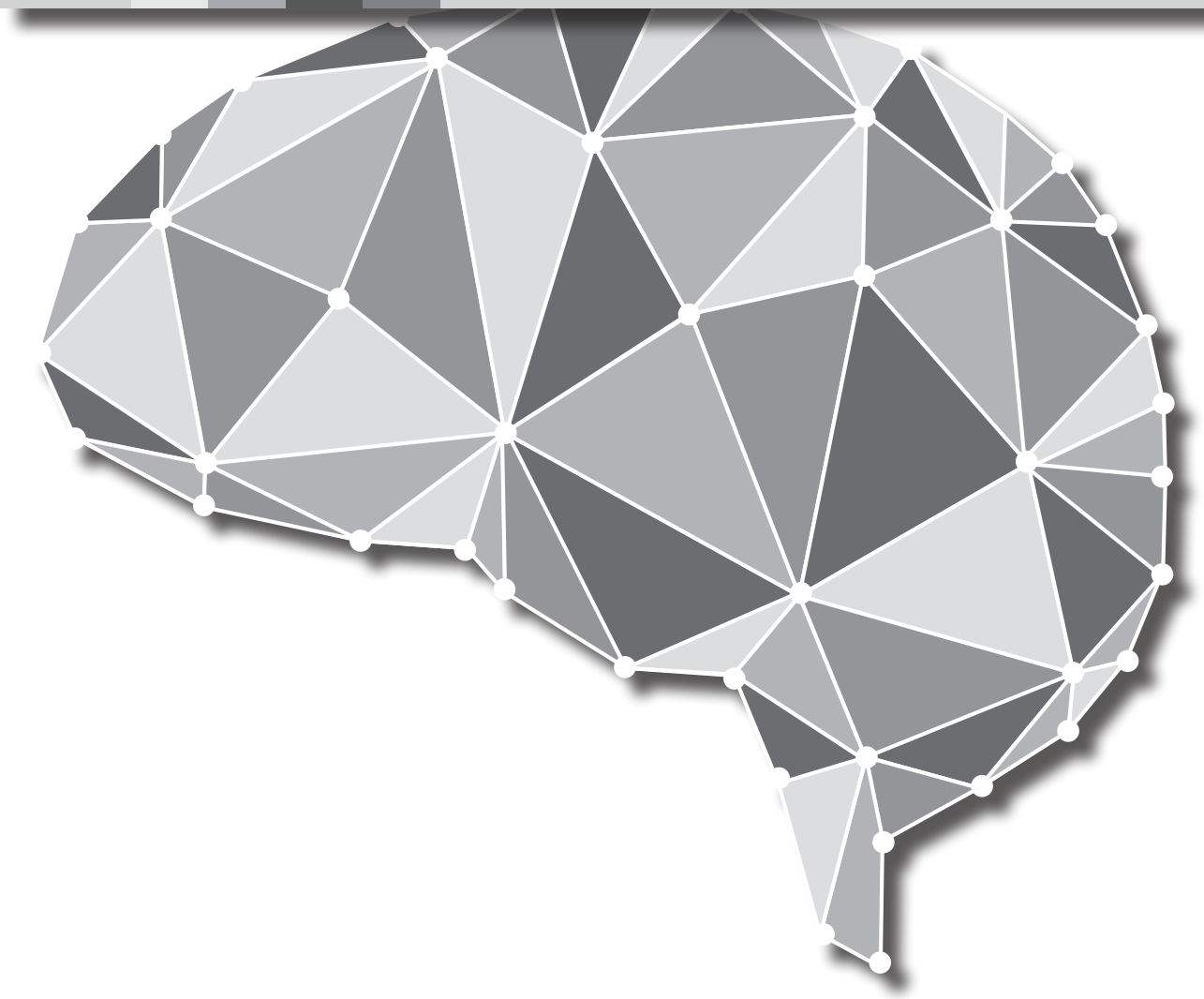
Journal of Clinical and Experimental Neuropsychology (2012), 34, 598-605



Abstract

The modified Telephone Interview for Cognitive Status (TICS-m) is a widely used screening instrument for (Alzheimer's) dementia. Psychometric evaluation of the TICS-m is limited.

This study examined the relation between the TICS-m and a comprehensive neuropsychological assessment in older persons (*n*=243) without cognitive deficits.

The TICS-m total score correlated with multiple cognitive domains (range *r*=0.22–0.49). Factor analysis of the TICS-m items yielded four interpretable factors: 'verbal memory', 'orientation/mental tracking', 'language/reasoning' and 'attention/working memory' which also showed (modest) correlations with the neuropsychological assessment (*r*=0.02–0.48). The TICS-m appears to reflect a 'general cognitive ability' rather than, for example, memory functioning alone.

Introduction

Screening tests for cognitive functioning are increasingly used for both clinical and research purposes. Most of these require face-to-face administration, which is not always feasible, particularly in the follow-up of older persons in research settings. To overcome this limitation, several telephone interview-based cognitive screening instruments have been developed (e.g. 1-3). The Telephone Interview for Cognitive status (TICS), developed by Brandt et al. (1), was modelled after the Mini Mental State Examination (MMSE) and is currently the most widely used telephone-based screening instrument. In the modified version of the TICS (TICS-m), a delayed verbal recall item was added, to better assess episodic memory in the detection of (early) Alzheimer's disease (4). Despite its popularity, some authors have raised concerns about the sensitivity of the TICS-m to detect milder forms of cognitive impairment (5,6). The TICS-m is purported to be a test of 'global' cognitive functioning; however, a systematic approach to item selection in the construction of the test is not described. In the absence of a thorough psychometric evaluation of the TICS-m, factor analysis has been performed to examine which cognitive constructs underlie TICS-m performance (7,8,5). The relation between the TICS-m and a comprehensive neuropsychological assessment has received even less attention. One previous study examined the relation between the TICS-m and a neuropsychological examination (9). It showed an association between the TICS-m composite score and several cognitive domains, but investigation of the cognitive functions measured *within* the TICS-m was not performed.

The present study examined the construct validity of the TICS-m in a large sample of older persons without known clinically manifest cognitive deficits, by investigation of the relation between the TICS-m and an extensive neuropsychological assessment and by means of factor analysis of the TICS-m items. Examination of this relation in a relatively healthy sample of persons gives an evaluation of the association between these two measures that is unbiased by confounding variables such as disease severity. The study aims to provide insight into two important questions. Does the TICS-m provide a valid reflection of cognitive functioning as measured with a neuropsychological test battery in this group? How are the TICS-m and its underlying constructs related to different cognitive domains in a neuropsychological assessment?

Methods

Participants

The present study included 243 participants (81 persons without and 162 persons with type 2 diabetes) who were enrolled in two longitudinal studies on cognitive functioning in type 2 diabetes (Utrecht Diabetic Encephalopathy Study, UDES (10); Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care, ADDITION (11)). All participants with diabetes were recruited from a primary care setting. Persons without diabetes were recruited among the spouses or acquaintances of these patients. Participants had to be functionally independent and Dutch speaking. Exclusion criteria were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, a history of alcohol or substance abuse, and a fasting blood glucose ≥7.0 mmol/l for those without diabetes. Persons with known dementia were also excluded. Both the UDES and the ADDITION study entailed cognitive assessment at baseline and after 3-4 years; the TICS-m was administered at the follow-up assessment. Thus, for the present analysis, all 243 participants who performed both the neuropsychological examination and the TICS-m at follow up were included (84% of the baseline UDES sample, 56% of the baseline ADDITION sample). Both studies were approved by the local medical ethics committees and were completed in accordance with the guidelines of the Helsinki Declaration.

The neuropsychological assessment was identical in both studies. To control for possible material-specific learning effects at the follow-up examination, parallel versions were used for memory tests. The results of both studies have been described previously (10,11). Briefly, compared to the control group, the patients with type 2 diabetes showed modest cognitive decrements, mainly in memory (11), processing speed, and executive functioning (10). None of the included participants had cognitive deficits that impaired independent daily functioning, and effect sizes for the between-group differences in cognition were generally small to medium (0.2 to 0.5).

Measures

Participants performed an extensive neuropsychological examination either at the university hospital or at home, after which they completed the Dutch version of the TICS-m by telephone (12,4). The majority of the participants performed the TICS-m within one month after the neuropsychological assessment, but no later than after six months. The TICS-m has 23 questions, scored as 12 items with a maximum score of 50 (Table 1). The neuropsychological assessment consisted of 11 standard verbal and nonverbal tasks, administered in a fixed order that took about 90 min to complete. The tasks were divided into five cognitive domains to reduce the amount of neuropsychological variables in the analysis and for clinical

clarity. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak, Howieson, & Loring (13) and not by formal factor analysis, to closely resemble everyday clinical practice. The domain *abstract reasoning* was assessed by Raven Advanced Progressive Matrices (12-item short form). The number of correct responses was recorded. The domain *memory* was divided into four subdomains (*working memory, immediate memory and learning rate, forgetting rate,* and *incidental memory*). *Working memory* was assessed by the forward and backward Digit Span of the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) and the Corsi Block-Tapping Task. The product score of the maximum span length times the number of correctly recalled sequences was recorded. *Immediate memory and learning rate* was assessed verbally and non-verbally with the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) and the Location Learning Test (LLT). For the RAVLT, the mean of the total number of words remembered in five learning trials was recorded, and a learning index was calculated as an estimate of the learning curve. For the LLT, both the total number of displacements over five trials and a learning index was calculated. *Forgetting rate*, as a measure of decay over time, was also calculated in the RAVLT and the LLT, in which the scores in the delayed recall condition were corrected for the score obtained in the fifth learning trial. *Incidental memory* was measured with the delayed recall trial of the Taylor Complex Figure Test. This score was also corrected for the score obtained in the copy condition. The domain *information processing speed* was assessed with the Trail Making Test - Part A (TMT-A), the Stroop Color-Word Test parts I and II, and the Digit Symbol subtest of the WAIS-III. For the TMT-A, the time to complete the task was recorded in seconds. For the Stroop Color-Word Test Parts I and II the mean of the total time (in seconds) to complete Part I and II was calculated, and the total correct number of copied symbols within two minutes was recorded for the Digit Symbol. The domain *attention and executive function* consisted of four subdomains (*response inhibition, divided attention, concept shifting,* and *verbal fluency*). *Response inhibition* was assessed by the Stroop Color-Word Test Part III. The time to complete this task was recorded in seconds and was corrected for the time to complete the Stroop Color-Word Test Part II. *Divided attention* was assessed with the Trail Making Test-Part B, controlling for performance on TMT-A. *Concept shifting* was assessed by the Brixton Spatial Anticipation Test where the number of errors was recorded. *Verbal fluency* was assessed both with a category-naming task (Animal Naming, 2 min) and two letter fluency tasks ('N' and 'A', 1 min each). The total number of correct responses was recorded. The domain *visuoconstruction* was assessed by the Copy trial of the Taylor Complex Figure Test.

The raw test scores were standardized into *z* scores per cognitive domain. These *z* scores were calculated by using the pooled mean of baseline scores of the whole study sample. The *z* score for each domain was derived by calculating the mean of the *z*-scores for tests

comprising that domain. A composite *z* score was also calculated by averaging the domain scores to represent 'global cognition'. Premorbid intelligence was estimated with the Dutch version of the National Adult Reading Test (14).

Table 1 Telephone Interview for Cognitive Status – Modified.

Item	TICS-m question	Points
1	Name (first, last)	2
2	Orientation (day of week, date, season)	5
3	Age & phone number	2
4	Counting backwards from 20 to 1	2
5	10-word list immediate recall	10
6	Count backward from 100 by 7s	5
7	Naming ('tool to cut paper?')	4
8	Repeat phrase ('postbankspaarboekje')*	2
9	Information ('present queen?')	4
10	Tap 5 times on phone	2
11	Opposites ('opposite of east?')	2
12	10-word list delayed recall	10
	Total score	50

*Example in English version: 'Methodist Episcopal'

Statistical analysis

Categorical variables were reported as numbers and percentages, continuous variables as means with standard deviations (*SD*s) and nonnormally distributed variables as median with interquartile range (IQR). The relation between the TICS-m total score and the cognitive domains was performed with Spearman rank correlation analysis (alpha <.01 was considered significant). Principal axis factoring with oblique (oblimin) rotation was used to examine the factor structure of the TICS-m items, using the roots greater than one criterion to determine the number of factors. Factor loadings greater than 0.30 were considered relevant in interpreting the factor. Correlations between TICS-m factor scores and cognitive domain scores were examined with Spearman rank correlation analysis. Because patients with type 2 diabetes were overrepresented in our sample, sensitivity analysis was performed adjusting the correlation analysis for diabetes status.

Bland and Altman illustrated in an influential paper that a high correlation does not necessarily mean that there is sufficient *agreement* between two measures (e.g. whether they give an equally high or low estimation of true values; 15). In secondary analyses, Bland-Altman plots were therefore used to examine agreement between performance on the TICS-m and the cognitive domains by plotting the mean of the two measurements (*x*-axis) against the difference between the measurements (*y*-axis; both expressed as standardized *z* scores) with

the accompanying 95% limits of agreement (15). These plots show a quantification of the differences between performance on the TICS-m and the neuropsychological assessment and provide an interval within which 95% of the differences between the two instruments are expected to lie. A narrow 95% interval indicates greater agreement between the TICS-m and the neuropsychological assessment.

Results

Table 2 shows the characteristics of the participants as well as the raw neuropsychological data. The distribution of the TICS-m scores in the total sample followed a normal distribution (Kolmogorov-Smirnov z = 1.03, p=0.24; skewness 0.001 ± 0.17, kurtosis -0.15 ± 0.34). The TICS-m score showed significant correlations with age (r=-0.16, p<0.05) and estimated IQ (r=0.39, p<0.001).

The correlations between the TICS-m total score and the neuropsychological domain scores are presented in Table 3. In the total study sample, the TICS-m score showed statistically significant correlations with all five cognitive domains and with the composite sum score (range 0.22 to 0.49). The correlation with visuoconstruction was lowest (r=0.22). Adjusting the correlation analysis for diabetes status yielded similar results (data not shown).

Table 2 Characteristics of the participants.

Characteristic	Total sample
n	243
Age	67.7 ± 5.7
Male sex: *n* (%)	127 (52)
Estimated IQ	100 ± 18
Educational level: median (IQR)	4 (4-5)
TICS-m total score	36.1 ± 4.5
TICS-m <28 points: *n* (%)	7 (3)
Neuropsychological assessment	
Raven APM (short form)	7.0 ± 2.5
WAIS-III Digit Span forward [a]	45.1 ± 22.1
WAIS-III Digit Span backward [a]	24.6 ± 18.1
Corsi Block-Tapping forward [a]	37.8 ± 12.0
Corsi Block-Tapping backward [a]	37.8 ± 14.2
RAVLT Total Trials 1-5	42.4 ± 11.3
RAVLT Delayed Trial	8.8 ± 3.2
RAVLT Recognition	28.7 ± 1.8
LLT Total Trials 1-5 [b]	21.7 ± 19.9
LLT Learning Index	0.59 ± 0.30
LLT Delayed Recall[b]	3.0 ± 6.8
Complex Figure Test - Copy	33.1 ± 3.1
Complex Figure Test - Delay	17.5 ± 6.0
Stroop Color Word Test I [b]	49.3 ± 9.3
Stroop Color Word Test II [b]	63.9 ± 12.5
Stroop Color Word Test III [b]	117.9 ± 39.3
TMT Part A [b]	42.6 ± 17.5
TMT Part B [b]	106.2 ± 58.9
WAIS-III Digit Symbol	56.7 ± 16.5
Letter fluency (mean N+A)	10.9 ± 4.5
Category fluency (Animals)	32.6 ± 9.7
Brixton Spatial Anticipation Test [b]	18.8 ± 6.1

Data are means ± standard deviations unless otherwise specified. IQR = interquartile range. APM = advanced progressive matrices. RALVT = Rey Auditory Verbal Learning Test. LLT = Location Learning Test. TMT= Trail Making Test. WAIS-III = Wechsler Adult Intelligenc Scale – Third Edition.
[a] Product score defined as span length × number correct; [b] Higher test scores reflect worse performance.

Table 3 Correlation analysis between TICS-m total score and cognitive domain scores in the total sample (*n*=243).

Cognitive domain	TICS-m total score
Information processing speed	.45**
Attention & Executive functions	.38**
Memory	.40**
Abstract Reasoning	.33**
Visuoconstruction	.22*
Sumscore	.49**

Unadjusted Spearman rank correlation coefficients, * p<0.01, **p<0.001

Principal axis factoring (PAF) with oblique (oblimin) rotation was used to examine the factor structure of the TICS-m items in the total sample (Table 4). The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.60, and Bartlett's test of sphericity was significant ($\chi^2(55) = 434.8$, p<0.001), indicating high sampling adequacy. Item 1 (first and last name) was dropped from the analysis as all participants showed the maximal score on this item. The PAF yielded a multicomponent solution consisting of four factors with Eigenvalues >1.0 that accounted for 57% of the variance. Items 5 and 12 (10-word list immediate and delayed recall) loaded high on the first factor, which could be regarded as a *verbal memory* factor (Eigenvalue 2.47, 22% of variance explained). The second factor encompassed high loadings for items 2 (orientation), 4 (counting backwards) and 10 (tapping), which could be regarded as an *orientation/mental tracking* factor (Eigenvalue 1.46, 13% variance explained). Items 7 and 11 (naming, opposites) showed high negative loadings high on the third factor. These factor loadings were reversed to aid interpretation, after which the third factor could be regarded as *language/reasoning* (Eigenvalue 1.25, 11% of variance explained). The final factor encompassed high loadings for items 6 and 8 (counting backwards in 7s, repeat phrase), which could be regarded as an *attention/working memory* factor (Eigenvalue 1.04, 10% of variance explained). Items 3 and 9 showed negligible factor loadings. In secondary sensitivity analysis, the factor analysis was repeated in persons with and without diabetes separately, both of which yielded four-factor solutions that were highly similar to the primary analysis (data not shown).

Table 4 Factor loadings of principal axis factoring of the TICS-m items.

TICS-m item	Verbal memory	Orientation / Mental tracking	Language / reasoning[a]	Attention / Working memory
	1	2	3	4
5	.79			
12	.97			
2		.37		
4		.44		
10		.50		
7			.65	
11			.60	
6				.44
8				.45
Eigenvalue	2.47	1.46	1.25	1.05
Variance explained	22%	13%	11%	10%

Factor loadings <0.30 removed. [a] Factor loadings for factor 3 were inversed for interpretation.

Table 5 shows the correlations between the factor loadings of the TICS-m factors and the domain scores of the neuropsychological test battery. Overall, these results show a rather non-specific pattern with correlations in the 0.20 to 0.50 range between information processing speed, attention and executive functions, memory and abstract reasoning, and all four TICS-m factors. For memory, it is noteworthy that the highest correlations are with the expected factors (i.e. memory correlates 0.33 with factor 'verbal memory' and 0.32 with factor 'attention/working memory'). Also, visuoconstruction was unrelated to factors 'verbal memory' and 'orientation/mental tracking'. Adjusting the correlation analysis for diabetes status yielded similar results (data not shown).

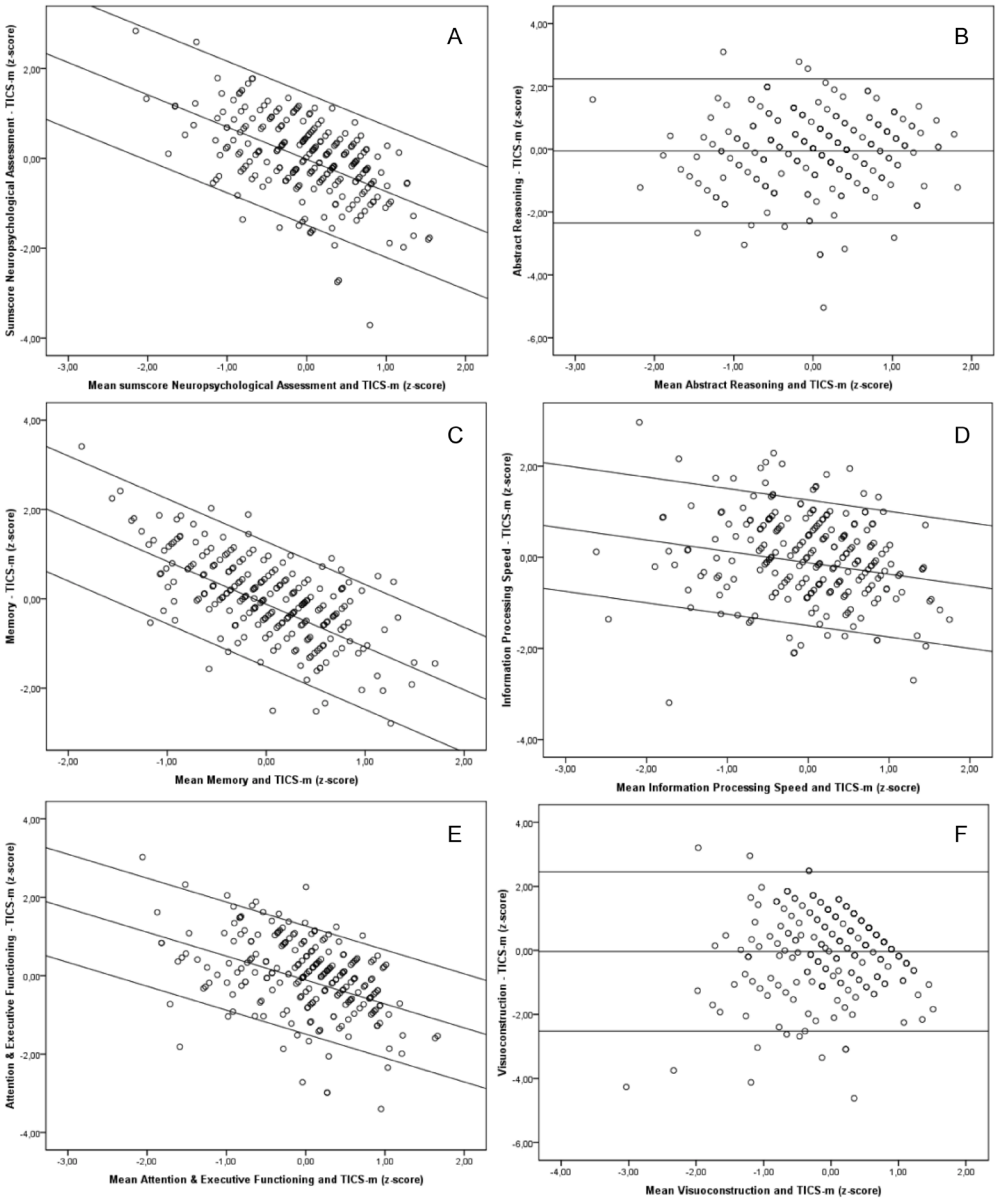
Table 5 Correlation analysis between TICS-m factors and cognitive domain scores.

Cognitive domain	Verbal memory	Orientation / Mental tracking	Language / reasoning[a]	Attention / Working memory
	1	2	3	4
Information processing speed	.40**	.27**	.22*	.40**
Attention and Executive functions	.32**	.43**	.21*	.48**
Memory	.33**	.20*	.16	.32**
Abstract Reasoning	.29**	.27**	.27**	.36**
Visuoconstruction	.14	.02	.23**	.24**

Unadjusted Spearman rank correlation coefficients, * p<0.01, **p<0.001
[a] Factor loadings for Factor 3 were inversed for interpretation.

Figure 1a-1f shows Bland-Altman plots comparing agreement between performance on the TICS-m and the neuropsychological assessment, with accompanying 95% limits of agreement. These plots show that the TICS-m total score may be up to 0.75 standard deviations above or below the composite *z* scores for the neuropsychological domains (Figure 1a). Similar limits of agreement are shown for the comparison between the TICS-m score and the individual cognitive domains (Figure 1). In individual persons these results indicate that compared to the neuropsychological assessment the TICS-m is able to detect cognitive *impairments* (defined as ≥1.5 *SD*s below average), but is less able to detect subtle decrements which are smaller in size (i.e. ≤0.75 *SD*s below average). Moreover, the negative relation that is depicted in Figures 1a and 1c-e indicate that for persons with low cognitive functioning (e.g. mean *z* score ≤ -2) the TICS-m slightly underestimates the performance compared to the neuropsychological assessment. For those with good cognitive functioning the TICS-m slightly overestimates the performance on the neuropsychological assessment, possibly reflecting a ceiling effect in the TICS-m.

Figure 1 Bland-Altman plots comparing TICS-m and neuropsychological assessment. Differences (*y* axis; neuropsychological assessment minus TICS-m) are plotted against means (*x* axis). All data are expressed as standardized z scores.



Discussion

The present study provides a detailed examination of the relation between a comprehensive neuropsychological assessment and a screening instrument for cognitive functioning that is administered by telephone (TICS-m) in a large sample of older persons without dementia. Overall, the results showed that the TICS-m is correlated with different cognitive domains (r=0.22–0.49), suggesting that in persons without marked cognitive deficits the TICS-m total score reflects a 'general ability' rather than a single cognitive function, such as verbal memory. The strongest associations were observed between the TICS-m total score and the domains information processing speed, attention and executive functioning, and memory, which are vulnerable to decline due to ageing or dementia (16). Factor analysis of the TICS-m items yielded four interpretable factors: 'verbal memory', 'orientation/ mental tracking', 'language/reasoning' and 'attention/working memory' that also showed (modest) correlations with the neuropsychological assessment (r=0.02–0.48). Furthermore, analysis of agreement showed differences between the TICS-m and the neuropsychological assessment up to 0.75 standard deviations, thereby indicating that the TICS-m can measure impairments that exceed this bandwidth (i.e. >2 *SD*s below the mean), as would be encountered in dementia, but the ability to measure more subtle cognitive decrements in individual persons may be limited. For screening purposes at the group level (provided that the sample size is large enough), this difference between the TICS-m and neuropsychological assessment would not necessarily lead to 'misclassifications' as there was only a slight bias (i.e., over- or underestimations) in the estimations of the TICS-m as compared with the neuropsychological assessment. One should keep in mind that formal evaluation of the sensitivity and specificity of the TICS-m was not performed in the present study because of the (relatively) healthy nature of the study sample.

One previous study examined the association between the TICS-m and a neuropsychological examination in 104 women >75 years of age participating in a longitudinal study to detect clinical dementia (9). Correlation analysis between the composite TICS-m-score and six distinct cognitive domains (derived from principal component analysis, PCA) showed modest but statistically significant correlations with measures of episodic memory and attention, but not with working memory or visuospatial processing, which is largely comparable to the results reported in the present study. Associations with information-processing speed, clearly demonstrable in the present study, were not found, probably because only a single speed measure was included.

Three previous studies performed factor analysis on the TICS-m to examine the underlying latent constructs in large samples of older persons (7, *n*=11.497, mean age ~66 years, 46% variance explained; 8, *n*=3506 females, mean age 78.8±3.3 years, 42% variance explained; 5, *n*=6090, age >65 years, 47% variance explained). In these studies three or four factors were extracted, all of which included a strong verbal memory factor, whereas the remaining factors vary somewhat in encompassing TICS-m-items and interpretation. The factor solution found in the present study, albeit with a smaller sample size, is consistent with these previous studies. Interestingly, the present factor solution explained more variance (57%), possibly reflecting the use of principal axis factoring (PAF), instead of the principal component analysis (PCA) that was used in the previous studies, which is more suitable to analyse factors that are intercorrelated (17), as is generally the case with cognitive data.

Strengths of this study include the detailed assessment of cognitive functioning by means of a comprehensive neuropsychological assessment in a relatively healthy study sample and the use of PAF to best suit the nature of the cognitive data. Limitations include possible heterogeneity in the study sample by inclusion of both diabetic and nondiabetic participants. In our view, this sample of persons without clinically significant cognitive impairments, which still included a relatively wide performance range in both the neuropsychological assessment and the TICS-m, provides valuable insight in the relation between the two measures that cannot be easily deduced from samples that include demented participants. Generalisation of these results towards populations with more prominent cognitive decline or dementia should, however, be done with caution. The cognitive domains in the neuropsychological assessment were determined a priori instead of with factor analysis. Previous studies by our group have shown that both patient and control samples show differential performance in these predefined domains (e.g., 19). This procedure was thus preferred over factor analysis on the data from the neuropsychological assessment, which, given the wide range of different test measures, often results in factors that are difficult to interpret and show weak resemblance to clinical practice. Additional support for the validity of this domain division was found in the present study showing significant correlations with some domains but not with others. The present study included follow-up data of two unrelated studies in which all participants performed a neuropsychological assessment two times (baseline and follow up) but the TICS-m only once (follow-up). One could argue that the analyses reported in the present study are influenced by learning effects on the neuropsychological assessment. While this may have been the case for cognitive testing in general (participants are no longer 'naïve' to a testing-situation), material-specific learning effects were prevented by the use of parallel versions. Finally, although the correlation analysis showed statistically significant results, the total amount of explained variance was fairly modest, indicating that other variables may play a substantial role as well.

In sum, the TICS-m, which is primarily used as a screening instrument for dementia, shows modest correlations with a comprehensive neuropsychological assessment in older persons without dementia. It reflects multiple cognitive domains, or a 'general cognitive ability', and thus appears to give a qualitative assessment of cognition that is broader than memory functioning alone. Present results further indicate that, compared with a neuropsychological assessment, the value of the TICS-m lies mainly in detecting impairments rather than subtle decrements in cognitive functioning in individual persons.

Acknowledgements

The authors report no conflict of interest. EvdB and GJB were supported by Grant No. 2001.00.023 and 2003.01.004 of the Dutch Diabetes Research Foundation. The ADDITION study in the Netherlands was funded by grants from Novo Nordisk Netherlands, GlaxoSmithKline Netherlands and Merck Netherlands. The authors would like to thank the ADDITION Study Group (G.E.H.M. Rutten), the Utrecht Diabetic Encephalopathy Study Group (University Medical Center Utrecht), the "Utrecht Diabetes Programma (UDP)" and the "IJsselstein Diabetes Project" (mentor: Ph.L. Salomé) for their assistance.

References

1. Brandt, J., Spencer, M., & Folstein, M. (1988). The telephone interview for cognitive status. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 1,* 111-117.
2. Go, R. C., Duke, L. W., Harrell, L. E., Cody, H., Bassett, S. S., Folstein, M. F., et al. (1997). Development and validation of a Structured Telephone Interview for Dementia Assessment (STIDA): the NIMH Genetics Initiative. *Journal of Geriatric Psychiatry and Neurology, 10,* 161-167.
3. Roccaforte, W. H., Burke, W. J., Bayer, B. L., & Wengel, S. P. (1992). Validation of a telephone version of the mini-mental state examination. *Journal of the American Geriatrics Society, 40,* 697-702.
4. Welsh, K., Breitner, J., & Magruder-Habib, K. (1993). Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 6,* 111-117.
5. Lines, C. R., McCarroll, K. A., Lipton, R. B., & Block, G.A. (2003). Telephone screening for amnestic mild cognitive impairment. *Neurology, 60,* 261-266.
6. Yaari, Y., Fleisher, A. S., Gamst, A. C., Bagwell, V. P., & Thal L. J. (2003). Utility of the telephone interview for cognitive status for enrolment in clinical trials. *Alzheimer's & Dementia, 2,* 104-10.
7. Brandt, J., Welsh, K. A., Breitner, J. C. S., Folstein, M., Helms, M., & Christian, J.C. (1993). Hereditary influences on cognitive functioning in older men: a study of 4000 twin pairs. *Archives of Neurology, 50,* 599-603.
8. Buckwalter, J. C., Crooks, V. C., & Petitti, D. B. (2002). A preliminary psychometric analysis of a computer-assisted administration of the telephone interview for cognitive status-modified. *Journal of Clinical and Experimental Neuropsychology, 24,* 168-175.
9. Crooks, V. C., Petitti, D. B., Robins, S. B., & Buckwalter, J. G. (2006). Cognitive domains associated with performance on the telephone interview for cognitive status: modified. *American Journal of Alzheimer's Disease and Other Dementias, 21,* 45-53.
10. van den Berg, E., Reijmer, Y. D., de Bresser, J., Kessels, R. P., Kappelle, L. J., & Biessels, G.J. (2010). A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. *Diabetologia, 53,* 58-65.
11. Ruis, C., Biessels, G. J., Gorter, K. J., van den Donk, M., Kappelle, L. J., & Rutten, G. E. (2009) Cognition in the early stage of type 2 diabetes. *Diabetes Care, 32*, 1261-1265.
12. Kempen, G. I., Meier, A. J., Bouwens, S. F., van Deursen J., & Verhey, F. R. (2007). The psychometric properties of the Dutch version of the Telephone Interview Cognitive Status (TICS) (Dutch). *Tijdschrift voor Gerontologie en Geriatrie, 38,* 38-45.
13. Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.
14. Schmand, B., Lindenboom, J., & van Harskamp, F. (1992). *Nederlandse Leestest voor Volwassenen (Dutch).* Lisse, the Netherlands: Swets& Zeitlinger.
15. Bland, J. M., & Altman, D.G. (1986). Statistical methods for assessing agreement between two methods of clinical assessment. *The Lancet, 1,* 307-310.
16. Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society, 16,* 754-760.
17. Pett, M. A., Lackey, N. R., & Sullivan, J. J. (2003). *Making sense of factor analysis: the use of factor analysis for instrument development in health care research.* Thousand Oaks, CA: Sage Publications.

18. van den Berg E., Dekker J.M., Nijpels G., Kessels R.P.C., Kappelle L.J., de Haan E.H.F., Heine, R.J., Stehouwer, C.D.A., & Biessels, G.J. (2008). Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: The Hoorn Study. *Dementia and Geriatric Cognitive Disorders, 26*, 261-269.

CHAPTER 9

The impact of self-reported depressive symptoms on memory function in neurological outpatients

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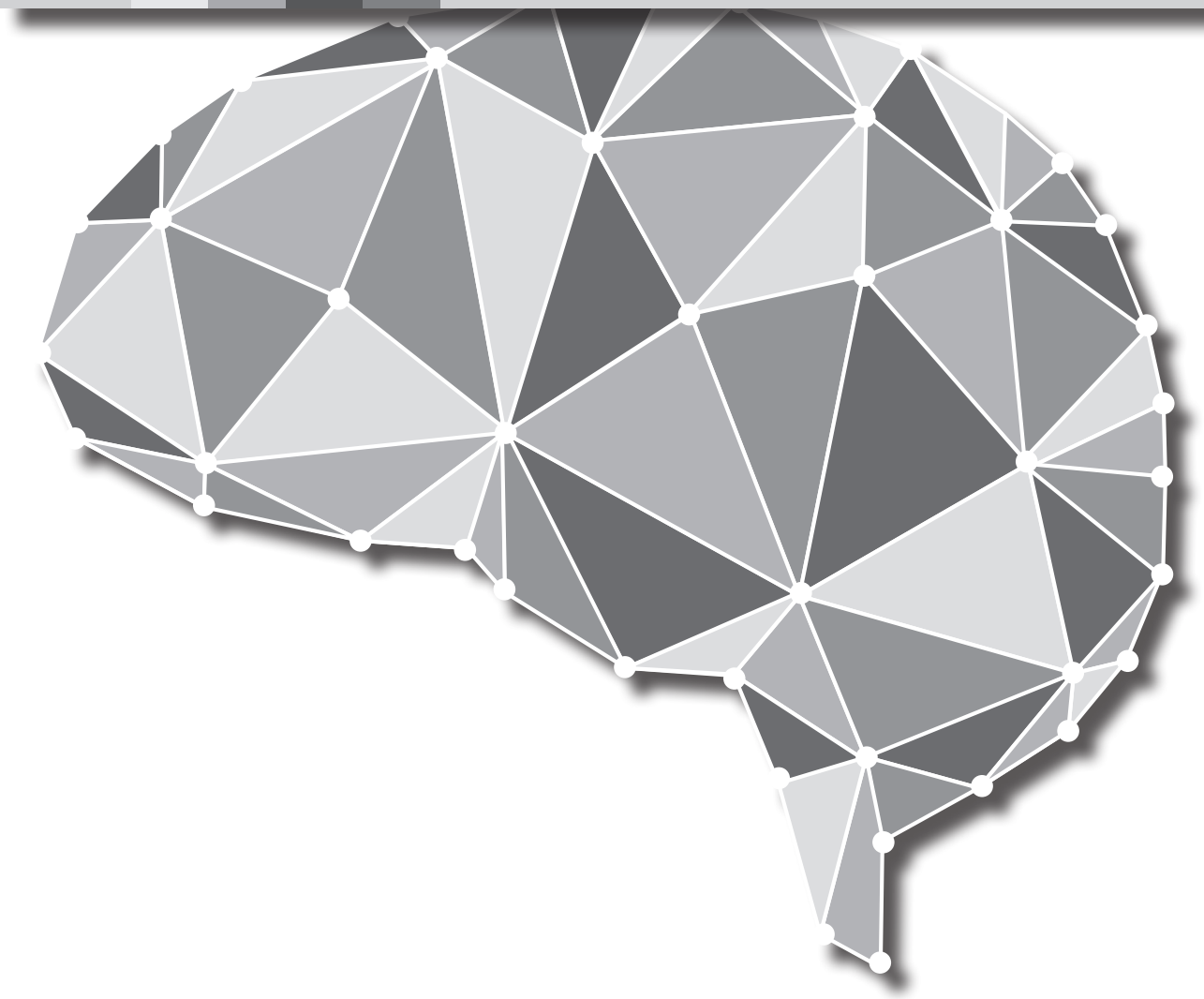
Clinical Neurology and Neurosurgery (2007), 109, 323-326



Abstract

The aim of this study was to examine the effect of self-reported depressive symptoms on memory function in a non-psychiatric, non-litigation outpatient sample and to identify which memory tests may be most susceptible for depression-related decline.

Self-reported depressive symptoms were measured by the Beck Depression Inventory (BDI-II) and memory function was assessed using a wide range of neuropsychological memory tests (digit span, word-list learning, visuospatial learning, incidental memory, story recall). Patients who visited the neurological outpatients clinic and were referred for a neuropsychological examination were included (*N*=50).

Correlation analyses showed that the BDI-II was significantly correlated with immediate story recall, delayed verbal recognition and the digit span. Furthermore, patients with mild or moderate-to-severe depressive symptoms performed worse than non-depressed patients on immediate story recall, but not on any of the other memory tests.

Memory performance is only minimally disrupted in neurological outpatients with depressive symptoms compared to non-depressed outpatients. These results are discussed in relation to limited mental effort and weak encoding in patients with self-reported depressive symptoms.

Introduction

Depression may hamper cognitive functioning. Most studies on the relation between depression and cognitive dysfunction have been performed in psychiatric inpatients, i.e. patients fulfilling the DSM-IV-criteria for Major Depressive Disorder (MDD). Especially the memory domain is susceptible for cognitive decline in patients with MDD (1-3), in some cases even mimicking organic dementia syndrome (4). Generally, this depression-related cognitive decline is explained by the concept of mental effort. That is, patients with MDD may display little effort in the encoding of new information, resulting in poor memory performance (5). This concept is known as the "weak encoding" hypothesis of memory impairment in MDD (6). Although the underlying process may be unclear, it can be concluded that especially the acquisition of new information is impaired in MDD, which is probably related to limited processing capacity.

Little is known about memory function in non-psychiatric patients with self-reported depressive symptoms. A recent study has examined a large group of neurological patients, showing no differences on cognitive function between patients with mild and patients with severe depressive symptoms, using the Beck Depression Inventory (BDI) (4). All these participants were involved in litigation and were examined for compensation-seeking purpose. Since compensation-seeking patients are often showed to perform poorly on tests of symptom validity (7), this sample is not comparable to the general neurological outpatients who are referred for neuropsychological assessment. This is illustrated by the fact that 41.6% of their patients had to be excluded from the analyses because of suboptimal performance on malinger tests (4).

Furthermore, information is lacking about which specific memory tasks are most susceptible for impaired performance in relation to depressive symptoms in neurological patients. This is relevant in the interpretation of neuropsychological test results in patients with depressive symptoms. Hence, the aim of the present paper was twofold. First, we examined the effect of self-reported depressive symptoms on memory function in patients from the outpatient clinic of neurology who were referred for neuropsychological examination and who were not involved in a litigation procedure. Since cerebral dysfunction in itself may result in cognitive impairment, we compared neurological patients with and without depressive symptoms on memory function rather than including a control group of healthy participants. Secondly, we compared the performances of these patients on a wide range of memory tests to investigate which tests may be susceptible for depression-related decline.

Patients and methods

In a retrospective design, we analysed a subsample of patients who visited the outpatient neurology clinic of the University Medical Center Utrecht, The Netherlands, between October 2003 and May 2006. Cases were anonymously analysed from a database containing all relevant variables that were collected in standard clinical practice, according to medical ethical guidelines. Inclusion criteria were: 1) patients had to be referred for neuropsychological assessment diagnostic reasons by their neurologist on the basis of cognitive complaints and were not involved in litigation, 2) patients had to pass symptom validity testing as examined with the Test of Memory Malingering or the Amsterdam Short-Term Memory Test (8), and 3) the memory tests listed below had to be included in the neuropsychological examination During this period, 343 patients were referred for neuropsychological testing. All patients who were referred to the neuropsychology unit completed the Beck Depression Inventory – Second Edition (BDI-II) (9). Of these, 50 patients were selected who fulfilled the inclusion criteria. This mixed-aetiology sample consisted of patients with cerebrovascular disease (*N*=9), head injury (*N*=6), memory complaints in the context of mild cognitive impairment or dementia (*N*=3), memory complaints of unknown origin (*N*=22), alcohol abuse (*N*=1), epilepsy (*N*=4), brain tumour (*N*=3), and other neurological disorders (*N*=2). Aetiology was determined at the time of testing. Education level was recorded using seven categories, 1 being the lowest (less than primary school) and 7 the highest (academic degree). BDI-II scores were used to classify these patients on the basis of cut-off scores described in the test manual. These cut-off points were determined using the receiver operating characteristic curve based on a group of patients with mild, moderate or severe depression according to the DSM-IV criteria and a group of healthy non-depressed controls to obtain optimal sensitivity and selectivity [9]. We subdivided the patients into three groups: no depression (BDI-II < 13; *N*=19 [16 males]; mean age 54.3 [SD = 11.8]; median education level: 6), mild depressive symptoms (BDI-II between 14 and 19; *N*=15 [9 males]; mean age 51.8 [SD = 13.4]; median education level: 6) and moderate-to-severe depressive symptoms (BDI-II > 20; *N*= 16 [9 males]; mean age 49.4 [SD = 14.0]; median education level: 6). The three groups did not differ with respect to age ($F(2,47) = 0.6$), education level (Kruskal-Wallis Test: $\chi^2(2) = 1.9$) and sex distribution ($\chi^2(2) = 3.7$).

Detailed neuropsychological assessment of the memory domain was performed focusing on working memory, verbal learning, visuospatial learning, story recall and incidental learning using standard neuropsychological tests. The Digit Span subtest of the Wechsler Adult Intelligence Scale-III was used to assess working memory (8). The Rey Auditory Verbal Learning Test (RAVLT) (10) was included to assess word-list learning, in which 15 words were presented in five subsequent trials, each followed by a free recall test (total score reflects

total number of remembered words for the five learning trials). After a 20-minute delay, a free recall test was performed, as well as a recognition test with the 15 targets and 15 new distracter items. The modified Location Learning Test was used to assess visuospatial learning (11); the total score reflects the total deviation score over the five learning trials. The delayed score is the difference between the performance after a 30-min delay compared to the last learning trial. A modified Story Recall test based on the stories from the Rivermead Behavioural Memory Test (8) was performed to assess prose memory. In this test, the patients heard two short stories (A and B), each followed by a free recall test (total score is number of remembered phrases from both stories). After a 15-minute delay, a free recall trial was performed to assess decay (% remembered compared to immediate recall). Finally, the Rey Complex Figure Test (8) was included as a measure of visuospatial incidental learning (% recalled after delay compared to the copy trial).

Correlations (Pearson's *r*) between the BDI-II raw scores and the memory test scores were computed to study the relation between the level of depressive symptoms and performance of memory tests independent from the depression classification. Subsequently, multivariate analysis of variance was performed with Group (three levels) as between-subject factor and the different test scores as dependent variables to investigate whether mildly depressed patients and patients with moderate-to-severe depression differ in memory performance from non-depressed patients. Post-hoc univariate analyses of variance were performed for tests that showed statistically significant group differences on the multivariate analyses, with the no depression group as reference.

Results

Table 1 shows the performance on the memory tests for the three groups of patients and the correlation coefficients between the memory measures and the raw BDI-II score for the whole patient group taken together. Correlation analyses demonstrated significant negative correlations with the forward score on the Digit Span ($p < 0.05$), the delayed recognition trial of the RAVLT ($p < 0.01$) and the immediate Story Recall test ($p < 0.0005$). None of the other correlations were statistically significant. Furthermore, multivariate analyses showed a main effect for group on the immediate recall score of the Story Recall test ($F[2,47] = 6.5$, $p < 0.003$). Post-hoc two-tailed Dunnett *t*-tests showed that compared with the group without depression, the mild depression group ($p < 0.05$) and the moderate-to-severe depression group ($p < 0.002$) performed worse. No multivariate group differences were found on any of the other memory measures (all *F*-values < 1.7).

Table 1 Correlations (Pearson's *r*) between the BDI-II raw score and the memory tests, performance (mean + SD) on the memory tests for the three patient groups (higher scores indicate better performance), as well as exact statistics for the multivariate analyses and level of significance for the post-hoc univariate between-group analysis (no depression group as reference).

Memory test	Correlation with BDI-II raw score	No depression (BDI ≤ 13)	Mild depression (14 ≤ BDI ≤ 19)	Moderate-to-severe depression (BDI ≥ 20)	F(2,47)	p-value
Digit Span (WAIS-III)						
Forward score	-0.28*	8.7 (2.0)	7.9 (2.3)	7.9 (1.2)	1.1	0.34
Backward score	-0.21	6.3 (2.2)	5.0 (2.2)	5.8 (1.7)	1.7	0.20
Rey Auditory Verbal Learning Test						
Total immediate score	-0.04	38.8 (5.4)	35.9 (13.0)	36.9 (9.2)	0.5	0.65
Delayed recall	-0.03	6.7 (3.3)	5.8 (3.3)	6.4 (3.0)	0.4	0.70
Delayed recognition	-0.38**	27.8 (2.2)	26.9 (3.6)	26.2 (2.8)	1.5	0.24
Location Learning Test						
Total deviation score[a]	0.19	26.3 (15.2)	41.5 (36.2)	39.0 (27.3)	1.6	0.21
Delayed score (decay)[a]	0.15	-0.5 (2.7)	-0.5 (3.0)	-0.06 (5.9)	0.1	0.93
Modified Story Recall (RBMT)						
Total immediate score	-0.48****	21.7 (5.4)	17.2 (6.2)*	15.0 (5.2)***	6.5	0.003***
Delayed recall (% remembered)	-0.17	81.2 (18.2)	70.4 (22.6)	74.3 (10.6)	1.6	0.21
Rey Complex Figure Test						
Delayed recall (% remembered)	-0.09	54.6 (16.5)	46.3 (13.4)	47.6 (17.6)	1.3	0.27

[a] A higher test score indicates a worse performance for this memory test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.0005$

Discussion

This study showed that patients with neurological signs or symptoms who have report depressive symptoms have more problems with story recall than patients without depressive symptoms. No group differences on tests of working memory, verbal and visuospatial learning and incidental learning were found. Story recall tests may be regarded as memory tests requiring a high level of effortful attentional and mnemonic processing, as well as the ability to process a certain amount of contextually linked information within a short period of time. Thus, neurological patients with depressive symptoms only have difficulty with cognitively demanding memory tests compared to non-depressed patients, but not with memory tests that require less effortful processing, such as incidental learning or immediate recall of repeatedly presented information (i.e., list learning). This is in line with the "weak encoding" and mental effort hypotheses postulated in patients with MDD.

This is the first study to investigate the relation between memory function and depressive symptoms in a neurological patient sample that is not involved in litigation procedure. Our findings largely confirm previous results that showed no cognitive differences between compensation-seeking patients scoring either low (BDI < 10) or high (BDI > 25) on depressive symptoms [4]. This suggests that these previous finding extend to outpatients with neurological complaints who are neuropsychological examined outside a medical legal context.

Examining the relation between the level of depressive symptoms, regardless of depression category, and memory performance, evidence was found for negative correlations between the BDI-II score and the forward Digit Span, the delayed recognition trial of the RAVLT and the Story Recall immediate score. These memory tests are the most sensitive for depressive complaints. The forward Digit Span is a measure of attention. Since attention deficits may impair the acquisition of new information, this finding further supports the weak encoding hypothesis. The recognition trial of the RAVLT has been shown an index of the amount of effort that participants display in memory tasks (12). However, it should be noted that none of our patients showed any signs of insufficient effort or malingering on specific tests of symptom validity. Additionally, recent studies have shown that even in patients who perform poorly on a test of symptom validity, depressive symptoms were unrelated to test performance (13). Thus, although the present data show correlations between depressive symptoms and memory tests that can be regarded as effortful in some way, mental effort cannot fully explain depression-related cognitive decline.

In all, the findings show that especially immediate story recall, attention span and delayed verbal recognition are tasks that decline in patients with self-reported depressive symptoms. Although the present results are clinically useful in the interpretation of memory test performance in patients with neurological deficits and depressive symptoms, our sample size is modest and the aetiology of the patients is heterogeneous. Furthermore, since we evaluated patients who were referred for a neuropsychological examination for clinical purposes, our findings may suffer from selection bias. Still, we believe our sample is representative for the mixed patient group that is referred to a neurology department at a university medical centre. Moreover, neurological disease in itself may result in depressive symptoms that may have an "organic" basis, such as vascular depression or depression in the early stages of a dementia syndrome. However, it was not the aim to study in detail the effects of depressive symptoms on cognitive function in relation to the aetiology. Thus, future prospective studies should address the causality of the relation between cognitive deficits and depressive symptoms.

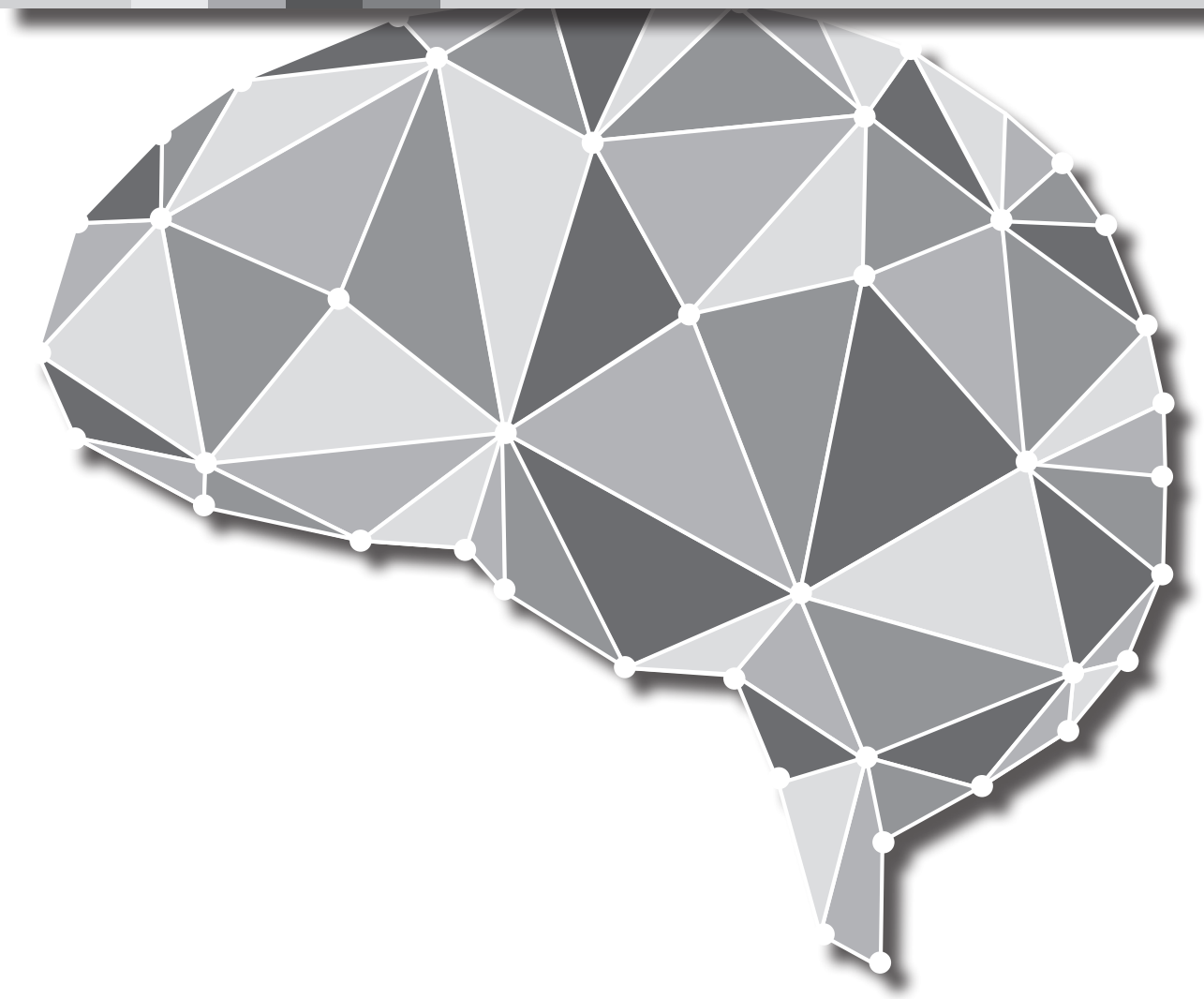
Although the BDI-II has very good psychometric properties, it must be emphasized that no extensive psychiatric examination occurred and that no statements can be made on the psychiatric diagnosis of these patients. In addition, no healthy control group was included, making it not possible to draw firm conclusions on the clinical relevance of the memory impairments themselves. Still, the present results are in agreement with previous findings suggesting that depressive symptoms in non-psychiatric patients have only a mild effect on memory performance compared to non-depressed patients. The present findings cannot answer the question whether the depressive symptoms may be a reaction to memory decline or disability, or whether both depressive symptoms and memory impairment are a direct result of cerebral dysfunction. While there is some evidence for the notion that depressive symptoms result in limited mental effort or weak encoding, resulting in lowered memory performance, future studies should focus in more detail on the causality of the relation between memory dysfunction and depressive symptoms in neurological patients.

References

1. Burt, D. Zembar, M., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin, 177*, 285-305.
2. Christensen, H., Griffiths, K., MacKinnon, A., & Jacomb, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society, 3*, 631-651.
3. Zakzanis, K.K., Leach, L., & Kaplan, E. (1999). Major depressive disorder. In: *Neuropsychological differential diagnosis*. Lisse, The Netherlands: Swets & Zeitlinger.
4. Rohling, M.L., Green, P., Allen, III L.M., & Iverson, G.L. (2002). Depressive symptoms and neurocognitive test scores in patients passing symptom validity tests. *Archives of Clinical Neuropsychology, 17*, 205-222.
5. Austin, M., Mitchell, P., Goodwin, G.M. (2001). Cognitive deficits in depression. *British Journal of Psychiatry, 178*, 200–206.
6. Weingartner, H., Cohen, R.M., Murphy, D.L., Martello, J., & Gerdt, C. (1981). Cognitive processes in depression. *Archives of General Psychiatry, 38*, 42-47.
7. Schmand, B., Lindeboom, J., Schagen, S., Heijt, R., Koene, T., & Hamburger, H.L. (1998). Cognitive complaints in patients after whiplash injury: the impact of malingering. *Journal of Neurology, Neurosurgery & Psychiatry, 64*, 339-343.
8. Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological assessment, 4th ed.* New York: Oxford University Press.
9. Beck, A.T., Steer, R.A., & Brown, G.K. (Van der Does, A.J.W., Trans.) (2002). *BDI-II-NL handleiding: De Nederlandse versie van de Beck Depression Inventory-Second Edition* [BDI-II-NL manual: The Dutch version of the Beck Depression Inventory-Second Edition]. Lisse, The Netherlands: Swets Test Publishers.
10. Van der Elst, W., Van Boxtel, M.P., van Breukelen, G.J., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society, 11*, 290-302.
11. Kessels, R.P.C., Nys, G.M.S., Brands, A.M.A., Van den Berg, E., & Van Zandvoort, M.J.E. (2006). The modified Location Learning Test: norms for the assessment of spatial memory function in neuropsychological patients. *Archives of Clinical Neuropsychology, 21*, 841-846.
12. Nelson, N.W., Boone, K., Dueck, A., Wagener, L., Lu, P., & Grills, C. (2003). Relationships between eight measures of suspect effort. *The Clinical Neuropsychologist, 17*, 263-272.
13. Yanez, Y.T., Fremouw, W., Tennant, J., Strunk, J., & Coker, K. (2006). Effects of severe depression on TOMM performance among disability-seeking outpatients. *Archives of Clinical Neuropsychology, 21*, 161-165.

CHAPTER 10

General discussion



This thesis provides examples of different purposes of a neuropsychological examination and it reflects the diversity of this instrument. Before discussing the findings and debate some practical implications, I will first summarise the main findings of the studies.

Summary

In **chapter 2** we illustrated, by means of a case report, how the diagnostic process in patients with Posterior Cortical Atrophy (PCA) can be delayed due to failure to recognize the true nature of the complaints expressed by the patient. In many cases, as in our patient, clinicians are searching for an ophthalmological disorder instead of a problem in the higher order visual functioning to explain patients' complaints. In this case, a neuropsychological examination was not considered until the patient also begun to suffer from memory problems. Specified neuropsychological tests for higher order visual functions during the examination were contributory in the diagnosis process of this patient.

Chapter 3 described a patient with severe cognitive disorders after incidental ecstasy use. By administrating multiple memory tests and by the use of an experimental virtual reality task we revealed a major memory and navigation disorder. Previous literature stated that sporadic ecstasy use was not harmful; this case report reopens the discussion about this topic.

In **chapter 4** we analysed the severity and pattern of psychiatric and psychosomatic complaints measured by the Symptom Checklist 90 in a neurological outpatient group. Neurological outpatients appeared to have a much higher level of complaints in comparison with healthy control subjects. The use of existing normative data from healthy control subjects in our patient group may result in inappropriate classifications.

Chapter 5 described the importance of being coached during an awake craniotomy. By studying patients' experiences during the awake craniotomy, we outlined what factors are important in coaching patients. The constant presence of the neuropsychologist during the procedure seemed to play a crucial role, even as a transparent communication.

The effectiveness of the errorless learning method in moderate to severe dementia patients was evaluated in **chapter 6**. After two learning trials, a beneficial effect was found. Nevertheless, this effect disappeared after a delay of ten minutes. This indicated limited applicability of the errorless learning method in this patient population.

In **chapter 7** we analysed cognitive functioning in diabetes mellitus type 2. Although we already knew a great deal about the relationship between this disease and cognitive disorders, it was still unclear at which stage these cognitive decrements started. An extensive neuropsychological examination in a large group of diabetes patients revealed that the decrements were already present at an early stage of the disease.

Chapter 8 described a psychometric evaluation of a frequently used telephonic cognitive screening instrument, the Telephone Interview for Cognitive Status (TICS). We analysed the relationship between the TICS and a comprehensive neuropsychological examination. Factor analyses revealed that the TICS reflect a general impression of cognition.

In **chapter 9** we investigated which memory test was most susceptible to the negative effect of depression. Depression yielded limited effects on memory performances, although we did find a worse performance in the immediate story recall in patients with mild to moderate-to-severe depressive symptoms in comparison with patients without depressive symptoms.

Discussion

Taken together, although each study was performed for its own specific goal, the studies in this thesis reflect a critical evaluation of diagnostic instruments and procedures, treatment programs, and factors of patient care. Moreover, the studies illustrate how the neuropsychological examination can be used in research settings. The different chapters illustrate the variety of purposes of the neuropsychological examination.

In the introduction section we subdivided our studies on the basis of the frame of reference offered by Lezak (Diagnosis, Patient Care, Treatment and Research) (1). As described previously, some studies were exemplary for illustrating the value of a neuropsychological examination in a diagnostic process. Other studies emphasised the importance of a neuropsychological examination in research settings; likewise, other chapters mostly adhered to treatment or patient care purposes. This classification may suggest that studies typically serve only a single circumscribed purpose. However, is the subdivision we made in the introduction section as strict as suggested? Is it sufficient to focus just on one purpose or should we consider multiple aspects?

As an illustration we will reconsider chapter 2, a case report concerning PCA. In this study we described a patient who was complaining for a long period about visual problems. Because ophthalmologists could not find any ophthalmic disorders his complaints were

not understood, that is, until further neuropsychological decay was evident and he was examined by a neuropsychologist. The extensive neuropsychological examination, with special attention for higher order visual functions, revealed that the complaints were not a result of an ophthalmic disorder, but were arising from problems in processing visual stimuli in the brain.

This study primarily shows that a neuropsychological examination can be of great value in a diagnostic process and therefore this chapter was placed in the Diagnosis section of this thesis. Nevertheless, the neuropsychological examination was also used for other purposes. Because the complaints of our patient were not recognised for a long period, it was important to give him extensive explanations about the origin of the problems. Our patient (and his family) had to understand the origin of his cognitive disorders so that realistic goals for the future could be set. Compensating strategies were discussed and furthermore, we debated about the impact of the diagnosis on psychological aspects such as mood. On basis of these additional activities, one could argue that this neuropsychological examination was also contributory to patient care. Moreover, by describing the cognitive disorders as comprehensively as possible, the neuropsychological examination could likewise be used in treatment planning and in finding a suitable rehabilitation program. As a result of the neuropsychological examination, our patient was referred to a specialised institute for patients with comparable visuospatial disorders. Finally, because PCA is seen quite infrequently in clinical care, this patient was also of interest for research. Studying this case in detail and sharing knowledge about it by means of writing a case report could be contributory in understanding the disease. Taken together, all four purposes described by Lezak were to some extent addressed in this study.

Reconsidering this chapter, and reconsidering the other studies in this thesis, we must conclude that the subdivision made in the introduction section is too strict. Within one neuropsychological examination, different purposes can be achieved. As neuropsychologists, we aim the most optimal use of our neuropsychological assessment. Should we therefore not continuously keep other purposes as the one defined in the referral question in mind as well?

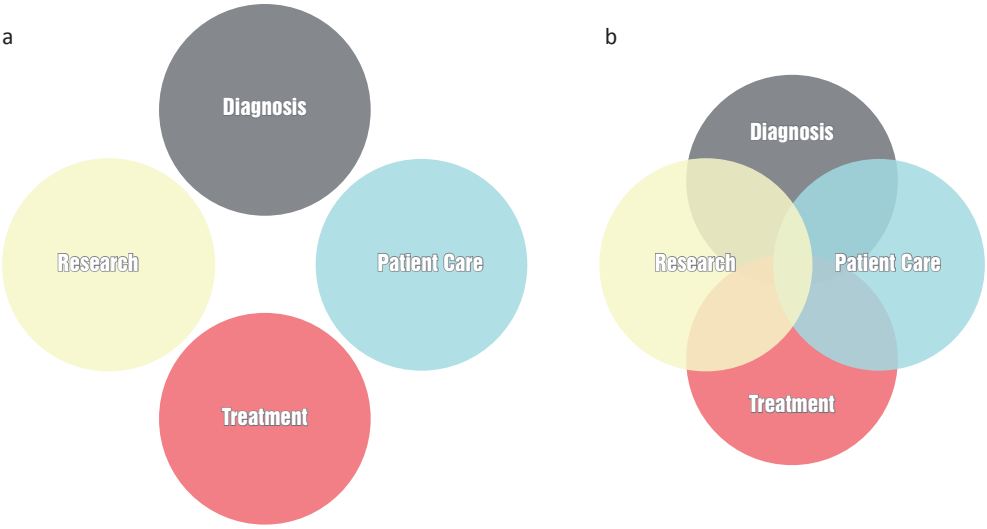
The multipurpose examination

Combining different purposes in one neuropsychological examination is described previously by Lezak as a **multipurpose examination:**

"Usually a neuropsychological examination serves more than one purpose. Even though the examination may be initially undertaken to answer a single question such as a diagnostic issue, the neuropsychologist may uncover vocational of family problems, or patient care needs that have been overlooked or the patient may prove to be a suitable candidate for research." (1)

This paragraph actually tells us that we should be aware of other possible purposes of the neuropsychological examination than originally determined. The multipurpose examination, or in other words a multifaceted approach, forces us to think outside the standard boundaries of our assessment and outside the original reason for referral.

Figure 1 Transition from four independent purposes of a neuropsychological examination to a multipurpose examination.

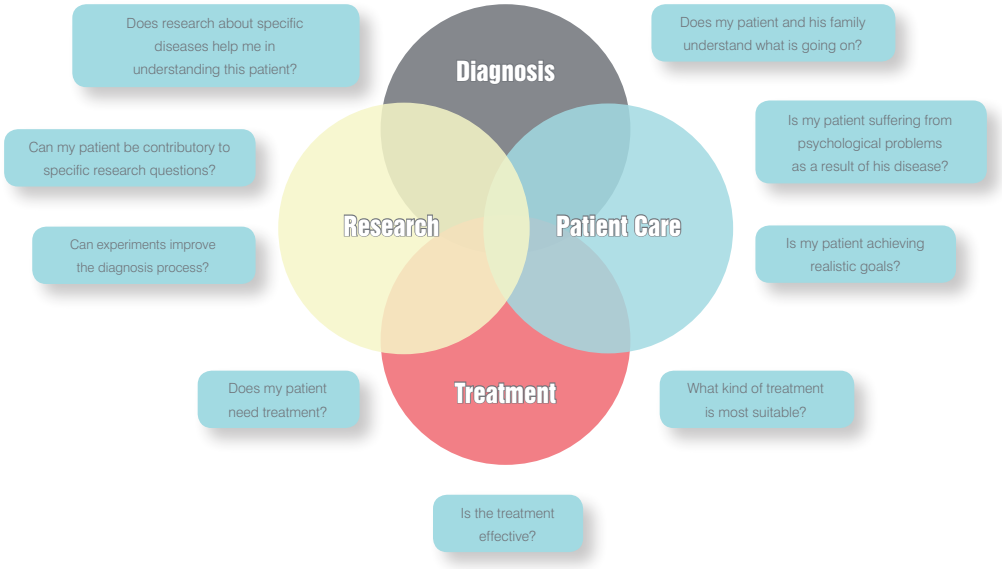


a: Diagnosis, Patient care, Treatment and Research as independent examination purposes.
b: A multipurpose examination. Integration of the four examination purposes; each purpose overlaps partly with the other three purposes.

In a multipurpose examination diagnosis, patient care, treatment, and research are more integrated. For example, when a neuropsychological examination is administrated for the purpose of diagnosis, the neuropsychologist should also critically consider issues of patient

care, treatment and research. Figure 2 gives examples of critical questions about all these areas, beyond the scope of diagnosis.

Figure 2 Critical questions concerning other purposes than the one defined in the referral question.



Research and clinical care (diagnosis, patient care, and treatment) may enforce each other in several ways. For example, case studies can have an enormous impact on our amount of knowledge about certain cognitive constructs (2). Although results from single case studies should be interpreted with caution, and special statistics may be necessary (3,4), they have taught us much about the underlying mechanism of our cognitive functioning. Descriptions of patients like H.M. (5) en Tan (6) have been of inestimable worth for the neuropsychology. The other way around, integrating experiments originally developed for research purposes in your examination in clinical care, can have several advantages. The experiments can be helpful in understanding the cognitive disorders and they can contribute in finding suitable rehabilitation programs (7). Chapter 3 of this thesis is a clear example of combining purposes for research and clinical care. The case report described in this study contributed to our knowledge about the relation between ecstasy use and cognition and the other way around, the use of an experimental task developed for research purposes was contributing to the diagnosis process of this patient.

Practical implications

In daily practice, the combination between the different purposes, or in other words between research and clinical care, is not always made. This can be the result of limited time and financial resources, but also simply because we are not used to it. This last reason will be debated in light of the neuropsychology curriculum in the Netherlands and in light of the daily practice of neuropsychologists. Finally, we will discuss the upcoming trend of working following evidence-based methods.

First of all, in the curriculum of neuropsychologists in the Netherlands, the integration of different purposes is not consistently made. The curriculum encompasses different and distinctive stages. At university students have to choose between a more clinical and a more fundamental research track. Subsequently, during the education program to become a certified psychologist (*opleiding tot Gezondheidszorgpsycholoog, GZ-opleiding*) almost solitary clinical issues are taught and there is no or just barely attention for a broader academic attitude (8). Only in the last stage, the study track to become a clinical neuropsychologist, research and clinical care are combined. Clinical care and research are thus artificially separated in different stages of the education system and only in a very late stadium reunited. The transition from one phase to another is not always a smooth one. The *GZ-opleiding* criticises that students do not have enough clinical experiences because the bachelor and master system focuses too much on research aspects. On the other hand, during the *GZ-opleiding,* almost no research aspects are instructed. Education at university and during the *GZ-opleiding* should be better in line with each other, as was also debated during the congress on the occasion of the 10-year anniversary of the *GZ-opleiding* (9). By combining clinical and research topics consequently in all stages of the neuropsychological educational program, neuropsychologists will be automatically more willing to integrate aspects of clinical care and research. The curriculum to become a clinical neuropsychologist can be leading in this discussion.

Furthermore, in the broad profession of neuropsychology, some neuropsychologists are still working in isolation, even when they are working within the same organisation. This may have several drawbacks. The diagnosis and treatment procedures are viewed as fragmented and the results of the neuropsychological examination are therefore not always optimally used. Furthermore, interesting cases for research will be missed because neuropsychologists working in clinical settings are not in contact with those who are participating in research. Short lines between hospitals, rehabilitation centres, nursing homes and research institutes will be helpful in combining the different purposes. An interesting example of such cooperation is a meeting at the University Medical Centre Utrecht for clinicians from

different institutes working with stroke patients. Neurologists, rehabilitation specialists, physiotherapists, neuropsychologists, employees of nursing homes and home-helpers participate in these meetings. Both research topics and topics about clinical care are debated. The primary aim of this meeting is to increase the quality of the whole treatment process. Beyond this primary goal, the neuropsychologist benefits from the intensive collaboration with other clinicians, which can be helpful in setting the neuropsychological examination in a broader scope than just the one of the referral. These kinds of meetings can be of great value in applying the multipurpose examination.

Jumping to a broader level than just the field of activity of the neuropsychologist in the Netherlands brings us to working following the standards of evidence-based methods. This method is illustrative in combining research and clinical care (and integrating the four purposes described by Lezak). Evidence-based methods find their origin in medical practice. In the need to objectively demonstrate the positive effects of procedures and treatments, *evidence-based medicine* was first described by the Evidence-Based Medicine Working Group in 1992 (10). It is defined as "the integration of best research evidence with clinical expertise and patient values" (11). The American Psychological Association developed a similar definition for its own profession: Evidence-Based Psychological Practice (EBPP) (12). More recently, a new term has been developed especially for neuropsychology, namely, Evidence-Based Clinical Neuropsychological Practice (EBCNP). Although the exact definition still needs to be further crystallised, aspects of clinical expertise, best outcomes research and the individual patient needs are integrated in this definition (13). The integration of the different purposes of a neuropsychological examination as described in this thesis can be found in this description. Fortunately, ENCNP is being used more and more often as a guideline, both in handbooks (1,14) and in clinical care. As suggested by Chelune (13), "*clinical questions should drive outcomes research as much as the latter informs practice*". Bowden et al. (2013) (15) describe how evidence based practice could be implemented in clinical practice.

The abovementioned practical implications may be contributory in realizing a multipurpose examination. However, to analyse what factors are determinative for neuropsychologists in achieving this multipurpose approach, more research is required. Future research amongst neuropsychologists could reveal whether limited time, restricted financial resources, and separation of clinical care and research during the study track are indeed obstacles in combing different purposes or if other factors also play a role.
Furthermore, the practical implications cannot be achieved in a short period. They require time, money and most importantly, awareness of the beneficial values. For now, this thesis makes neuropsychologists more aware of the different purposes of a neuropsychological

examination. Being aware of these different purposes can be helpful in looking outside the standard boundaries of your profession. When more and more neuropsychologists are doing this, neuropsychology will rise to a higher level.

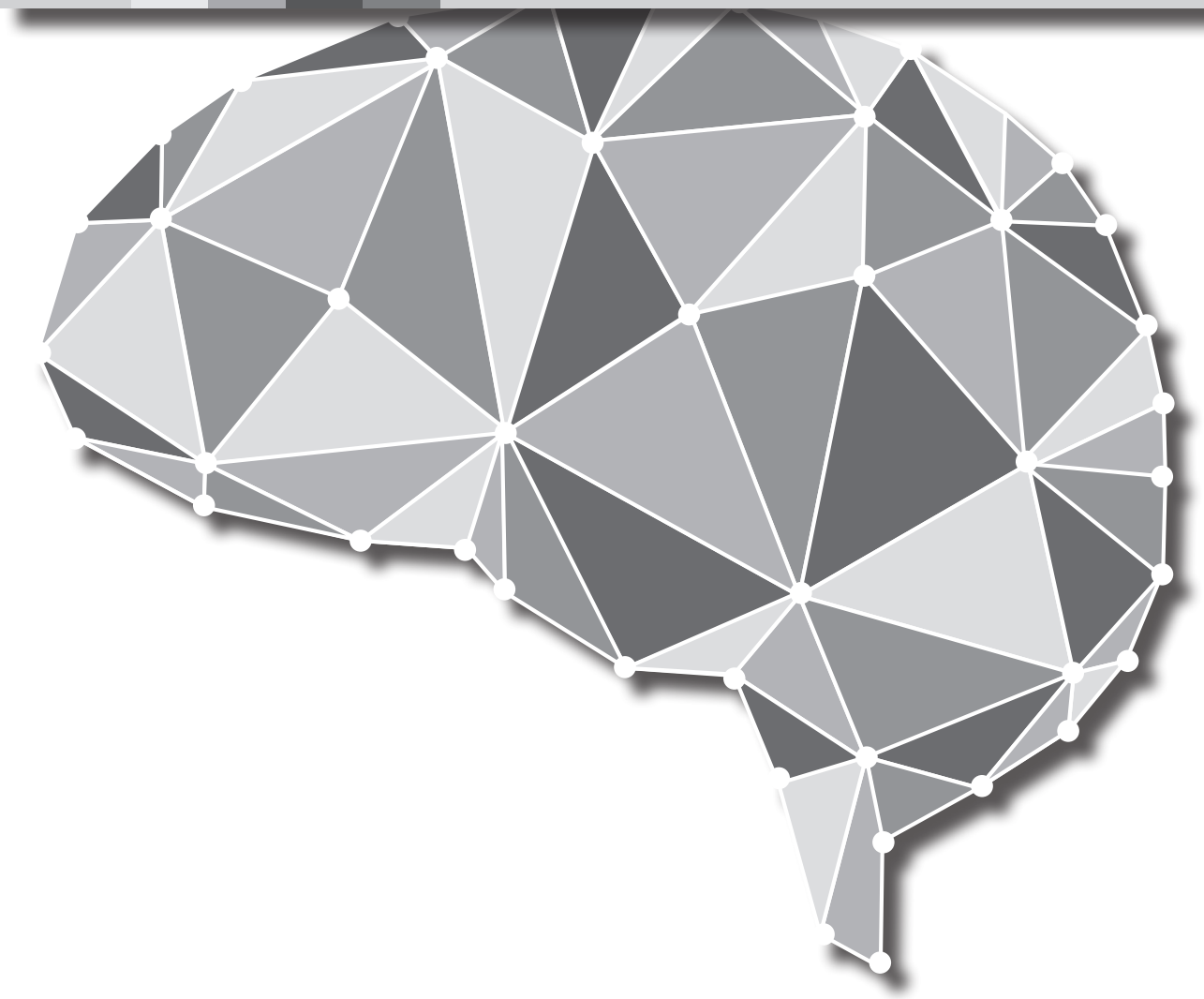
Personal reflection

The studies described in this thesis are the result of questions directly arising from work in clinical practice. My work at the University Medical Centre Utrecht and Utrecht University are a constant inspiration for new research topics. By writing this thesis I became more aware of the fundamental purposes of my work as a neuropsychologist. Knowledge about these different purposes made me more conscious of the beneficial value of integrating and combining these different purposes. Working at both an academic hospital and a university creates the ideal circumstances to aspire a multifaceted approach.

References

1. Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (2012). *Neuropsychological assessment*. New York: Oxford U.P.
2. Eling, P., & van Zandvoort, M. (2012). Neuropsychologie: de wetenschappelijke aanpak. In: Kessels, R., Eling, E., Ponds, R., Spikman, J., & van Zandvoort, M. (editors). *Klinische neuropychologie*. Amsterdam: Uitgeverij Boom.
3. Crawford, J.R., Gartwaite, P.H., & Ryan, K. (2011). Comparing a single case to a control sample: Testing for neuropsychological deficits and dissociations in the presence of covariates. *Cortex, 47*, 1166-1178.
4. Crawford, J.R. & Garthwaite, P.H. (2007). Comparison of a single case to a control or normative sample in neuropsychology: Development of a Bayesian approach. *Cognitive Neuropsychology, 24* (4), 343-372.
5. Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. *Seminars in Neurology, 4* (2), 249-259.
6. Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bulletin de la Sociéte Anatomique, 6*, 330-357.
7. Atzeni, T. (2012). The role of Experimentation in the daily practice of neuropsychological assessment: advantages and disadvantages. *Applied Neuropsychology: Adult, 19* (4), 249-256.
8. Postmaster opleiding tot gezondheidszorgpsycholoog, from http://www.rinogroep.nl/ pdf/ documentatie/folder_gz07_web.p
9. Vehmeyer, B. (2008). Tussen praktijk en wetenschap: 10 jaar GZ psycholoog. http://www.rino.nl/artikelen/tussen-praktijk-en-wetenschap
10. Evidence-Based Medicine Working Group (1992). Evidence-based medicine. A new approach to teaching the practice of medicine. *Journal of the American Medical Association, 268* (17), 2420-2425.
11. Sackett, D.L., Strauss, S.E., Richardson, W.S., Rosenberg, W., & Haynes, R.P. (2000). *Evidence-based medicine: How to practice and teach EBM (2nd ed.).* New York: Churchill Livingston.
12. APA Presidential Task Force on Evidence-Based Practice (2006). Evidence-based practice in psychology. *American Psychologist, 61* (4), 271-285.
13. Chelune, G.J. (2010). Evidence-based research and practice in clinical neuropsychology. *The Clinical Neuropsychologist, 24*, 454-467.
14. Schoenberg, M.R., Scott, J.G. (2011). *The little black book of neuropsychology*. New York: Springer.
15. Bowden, S.C., Harrison, E.J., & Loring, D.W. (2013). Evaluating research for clinical significance: using critically appraised topics to enhance evidence based neuropsychology. *The Clinical Neuropsychologist,* DOI: 10.1080/13854046.2013.776636

Nederlandse samenvatting



Neuropsychologie bestudeert de relatie tussen hersenen en gedrag. Lange tijd was dit vooral het werkgebied van neurologen en psychiaters. Pas rond 1980 werd neuropsychologie als zelfstandige discipline onderwezen aan de Nederlandse universiteiten. Inmiddels is neuropsychologie een snel groeiend vakgebied met een breed werkveld en zijn neuropsychologen werkzaam in verschillende instellingen, variërend van ziekenhuizen, revalidatiecentra, verpleeghuizen, forensische instellingen en onderzoeksinstituten.

Het belangrijkste instrument van de neuropsycholoog bij het in kaart brengen van gedragsuitingen als gevolg van onze hersenfuncties is het neuropsychologisch onderzoek. Dit onderzoek kan binnen verschillende kaders afgenomen worden. Eén van de belangrijkste handboeken binnen de neuropsychologie, "Neuropsychological Assessment" van Lezak, geeft een overzicht van de verschillende doelen van een neuropsychologisch onderzoek. Dit zijn:

1. Diagnostiek
2. Patiëntenzorg
3. Behandeling
4. Onderzoek

Dit proefschrift beoogt de diversiteit aan toepassingen van een neuropsychologisch onderzoek te laten zien. Dit wordt gedaan door een verscheidenheid aan studies te beschrijven. Alhoewel iedere studie is opgezet met geheel eigen specifieke doelen, reflecteren deze studies de primaire doelen zoals hierboven omschreven. De indeling zoals omschreven door Lezak wordt derhalve gebruikt om de studies binnen dit proefschrift te structureren.

Hoofdstuk 2 en 3 beschrijven de rol van het neuropsychologisch onderzoek binnen een **diagnostiek**proces. In hoofdstuk 2 wordt een patiënt beschreven waarbij het diagnostiek-proces fors vertraagd is doordat de zoektocht enkel gericht is op een oogheelkundige oorzaak voor zijn visuele klachten. Een neuropsychologisch onderzoek met specifieke aandacht voor hogere orde visuele functies leidt tot de diagnose Posterieure Corticale Atrofie, een subtype van de ziekte van Alzheimer die gekenmerkt wordt door problemen in de visuele verwerking. Hoofdstuk 3 beschrijft een patiënt die na incidenteel ecstasygebruik geheugen- en navigatieproblemen ontwikkelt die zelfs jaren na het drugsgebruik nog aanwezig zijn. Het neuropsychologisch onderzoek dat wordt afgenomen laat een zeer duidelijke geheugenstoornis zien. Omdat navigatieklachten moeilijk te objectiveren zijn met taken uit een standaard neuropsychologisch onderzoek wordt een experimentele *virtual reality* taak toegevoegd. Deze toevoeging blijkt zeer bij te dragen aan de diagnostiek van de klachten van de patiënt.

Hoofdstuk 4 en 5 illustreren de rol van een neuropsychologisch onderzoek binnen **patiëntenzorg**. Hoofdstuk 4 beschrijft het gebruik van een vragenlijst gericht op psychische en daarmee samenhangende lichamelijke klachten binnen een neuropsychologisch onderzoek. Het in kaart brengen van psychologische factoren is van groot belang in het kader van juiste diagnostiek of behandeling. Deze studie laat zien hoe neurologische patiënten scoren op de vragenlijst en bediscussieert het gebruik van de bestaande normen. Hoofdstuk 5 beschrijft de importantie van coaching tijdens wakkere hersenchirurgie. In de periode voorafgaand maar ook tijdens de ingreep wordt veel aandacht besteedt aan het meten van cognitieve functies door middel van neuropsychologisch onderzoek. Deze studie illustreert door middel van ervaringen van patiënten dat coaching eveneens een belangrijke rol speelt.

Hoofdstuk 6 is een illustratie hoe neuropsychologisch onderzoek gebruikt kan worden om de effectiviteit van een bepaalde **behandeling** in kaart te brengen. Binnen deze studie wordt gekeken naar de toepasbaarheid van een specifieke leermethode in een patiëntengroep met een matige tot ernstige vorm van dementie. Alhoewel er een effect van de leermethode gezien wordt, is dit slechts van kortdurende aard.

De laatste studies, hoofdstuk 7, 8 en 9, zijn voorbeelden hoe een neuropsychologisch onderzoek een rol kan spelen binnen wetenschappelijk **onderzoek**. Hoofdstuk 7 laat zien hoe een neuropsychologisch onderzoek gebruikt kan worden om binnen grote groepsstudies het cognitief functioneren van een bepaalde patiëntenpopulatie te onderzoeken. Deze studie laat zien dat al in een heel vroege fase van diabetes mellitus type 2 er milde cognitieve tekorten worden gevonden wanneer patiënten vergeleken worden met gezonde controles. Hoofdstuk 8 is een illustratie hoe een neuropsychologisch onderzoek een bijdrage kan leveren aan psychometrisch onderzoek naar bepaalde testinstrumenten. In deze studie wordt een frequent gebruikte telefonisch cognitief screeningsinstrument vergeleken met een uitgebreid neuropsychologisch onderzoek. Uit deze vergelijking komt naar voren dat het screeningsinstrument een indruk geeft van het globaal cognitieve functioneren. De laatste studie, hoofdstuk 9, is een voorbeeld hoe neuropsychologisch onderzoek gebruikt kan worden om verschillende stoorfactoren op het cognitief functioneren in kaart te brengen. Dit onderzoek laat zien welke geheugentaken het meest gevoeligheid zijn voor het effect van depressieve symptomen.

In hoofdstuk 10, de algemene discussie van dit proefschrift, wordt de indeling in verschillende doelen zoals hierboven omgeschreven ter discussie gesteld. Kunnen we deze doelen als losstaande factoren zien of zou een meer geïntegreerde visie beter zijn? Zouden we, wanneer we willen dat de resultaten van ons neuropsychologisch onderzoek zo optimaal mogelijk worden gebruikt, niet bij elk onderzoek alle vier de doelen in ons achterhoofd moeten hebben?

Het combineren van meerdere doelen binnen een neuropsychologisch onderzoek wordt door Lezak omschreven als een meervoudig doelen onderzoek. Hiermee wordt bedoeld dat een neuropsychologisch onderzoek meer dan één doel kan dienen. Alhoewel een onderzoek in eerste instantie voor één primair doel wordt afgenomen, bijvoorbeeld ten behoeve van een diagnostiekproces, kan de neuropsycholoog tegen andere doelen aanlopen die eerder niet onderkend zijn. Zo kunnen er zaken spelen die extra patiëntenzorg behoeven of kan een patiënt geschikt zijn voor wetenschappelijk onderzoek. Het meervoudig doelen onderzoek, of in andere woorden een onderzoek met een veelzijdige benadering, dwingt ons om buiten de standaard grenzen van ons werkterrein en buiten de primaire reden van aanvraag te denken.

In de praktijk wordt het combineren van meerdere doelen, of anders gezegd het combineren van klinische praktijk en wetenschap, nog niet altijd gedaan. Dit kan komen door beperkte tijd, financiële factoren of simpelweg doordat neuropsychologen het niet gewend zijn.

Het opleidingstraject van neuropsychologen binnen Nederland bestaat uit verschillende stadia. Op de universiteit kiezen studenten tussen een meer klinisch of juist meer onderzoekgericht traject. Tijdens de post-master opleiding tot Gezondheidszorgpsycholoog wordt veel aandacht besteed aan het klinische werk, maar is er slechts weinig aandacht voor wetenschappelijk onderzoek. Pas in de laatste fase van het opleidingstraject, de specialisatie tot Klinische Neuropsycholoog, worden klinische zaken en wetenschap geïntegreerd. Gedurende het gehele traject worden klinische aspecten en wetenschappelijk onderzoek dus uiteen getrokken om pas in een laat stadium weer gecombineerd te worden. Wanneer de integratie tussen de verschillende doelen consequent in elke opleidingsfase gemaakt zou worden zou de neuropsycholoog deze factoren automatisch meer combineren.

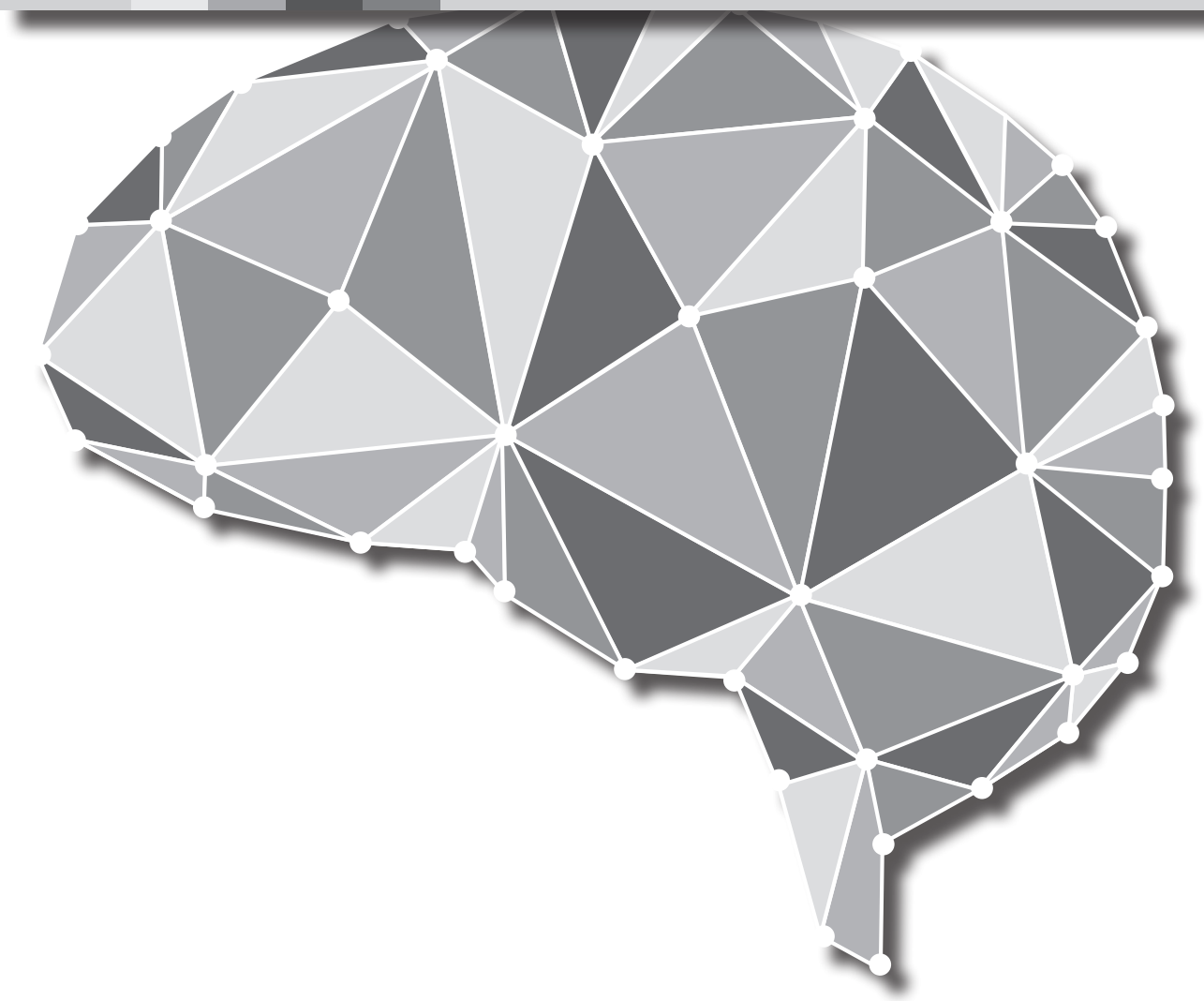
Wat verder meespeelt, is dat neuropsychologen binnen verschillende instellingen soms erg geïsoleerd kunnen werken. Dit maakt dat het diagnostiek- en behandeltraject als gefragmenteerd gezien kan worden waardoor de resultaten van een neuropsychologisch onderzoek niet optimaal gebruikt worden. Verder wordt interessante casuïstiek voor onderzoek gemist omdat neuropsychologen in de klinische praktijk niet in contact staan met wetenschappers. Kortere lijnen tussen ziekenhuizen, revalidatiecentra, verpleeghuizen en onderzoekinstituten zouden kunnen bijdragen aan het veelvuldiger combineren van verschillende doelen.

Bijdragend aan het integreren van de verschillende doelen is het werken volgens de *evidence-based* methode. Bij deze methode wordt gestreefd naar de integratie van wetenschappelijk bewezen resultaten, klinische expertise en de wens en mening van de

patiënt. Dit is illustratief in het verenigen van wetenschap en klinische zorg (en derhalve ook in het combineren van de vier doelen zoals omschreven in dit proefschrift; diagnostiek, patiëntenzorg, behandeling en wetenschap).

Dit proefschrift beoogt een bijdrage te leveren aan de bewustwording van neuropsychologen voor wat betreft de verschillende doelen van een neuropsychologisch onderzoek. Dit bewustwordingsproces kan er voor zorgen dat we vaker buiten de grenzen van onze eigen specialisatie kijken. Een veelzijdige benadering van het neuropsychologisch onderzoek zorgt ervoor dat de neuropsychologie naar een hoger niveau kan worden getild.

List of co-authors



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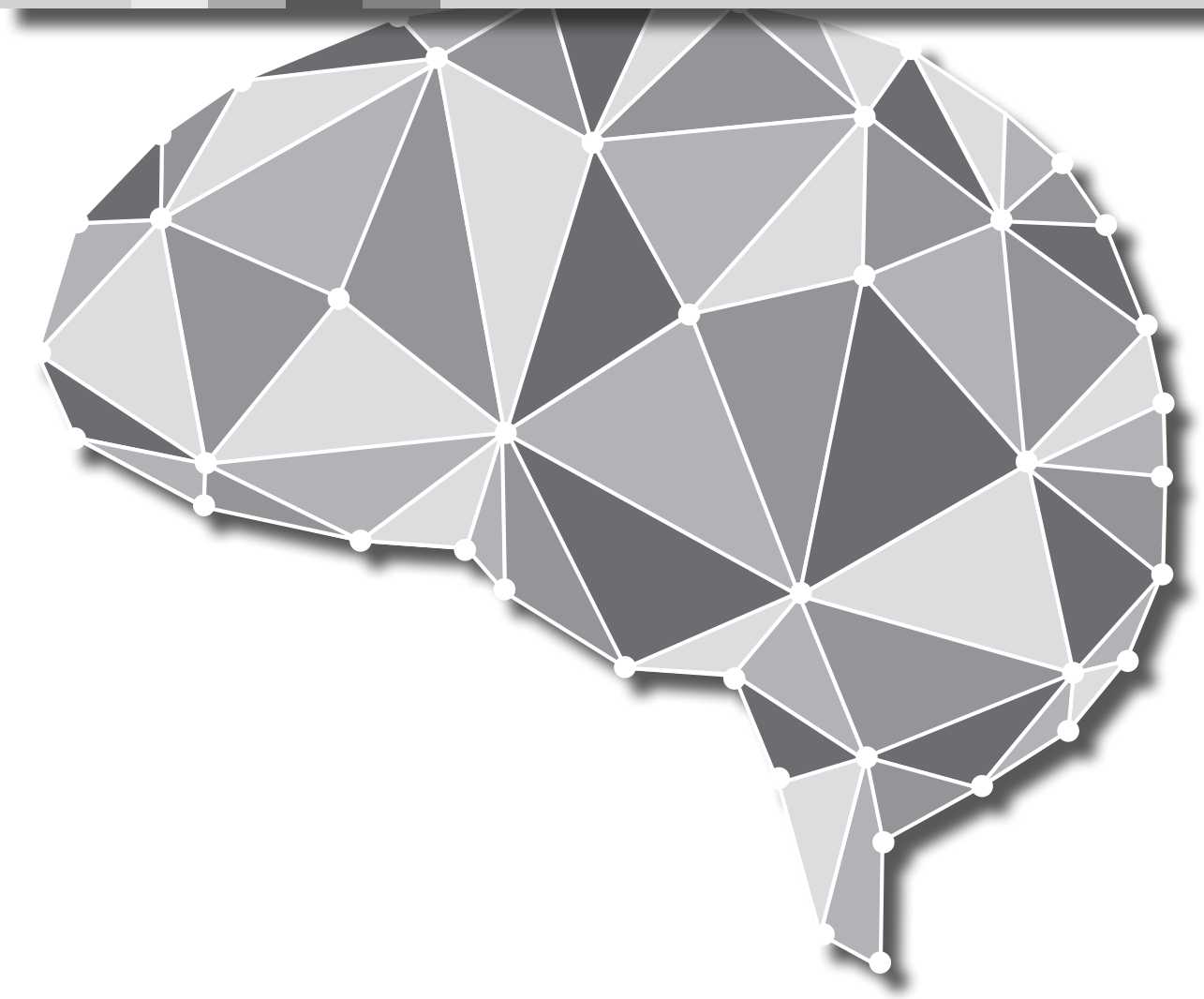
List of publications



Ruis, C., Postma, A., Bouvy, W., & van der Ham, I. (2014). Cognitive disorders after sporadic ecstasy use? A case report. *Neurocase,* DOI: 10.1080/23306343.2014.886398.

Ruis, C., van den Berg, E., van Stralen, H.E., Huenges Wajer, I.M.C., Biessels, G.J., Kappelle, L.J., Postma, A., & van Zandvoort, M.J.E. (2014). Symptom Checklist 90 – Revised in neurological outpatients. *Journal of Clinical and Experimental Neuropsychology*, DOI: 10.1080/13803395.2013.875519.

Ruis, C., Van den Berg, E., Van Stralen, H., Huenges Wajer, I., & Van Zandvoort, M. (2013). SCL-90: Misinterpretatie bij neurologische patiënten? *Tijdschrift voor Neuropsychologie, 8* (1), 46-52.

Van den Berg, E., Nys, G.M.S., Brands, A.M.A., **Ruis, C.**, van Zandvoort, M.J.E., & Kessels, R.P.C. (2013). Exploration of the Raven APM-National Adult Reading Test discrepancy as a measure of intellectual decline in older persons. *Applied Neuropsychology: Adult, 20* (1), 7-14.

Koekkoek, P.S., Rutten, G.E.H.M., **Ruis, C.**, Reijmer, Y.D., Van den Berg, E., Gorter, K.J., Stehouwer, C.D.A., Dekker, J.M., Nijpels, G., Kappelle, L.J., & Biessels, G.J. (2013). Mild depressive symptoms do not influence cognitive functioning in patients with type 2 diabetes. *Psychoneuroendocrinology, 39* (3), 376-386.

Ruis, C., Van den Berg, E., Van Zandvoort, M.J.E., Boshuisen, K., & Frijns, C.J.M. (2012). Ophthalmic impairment or higher-order visual deficit? Posterior cortical atrophy: a case report. *Applied Neuropsychology: Adult, 19*, 153-157.

Kessels, R., van den Berg, E., Nys, G., **Ruis, C.**, & Brands, I. (2012). De Location Learning Test (LLT-R): Het meten van het visueelruimtelijke episodische geheugen. *De Psycholoog*, *47*, 47-54.

Van den Berg, E., **Ruis, C.**, Biessels, G.J., Kappelle, L.J., & Van Zandvoort, M.J.E. (2012). The Telephone Interview for Cognitive Status (Modified): relation with a comprehensive neuropsychological assessment. *Journal of Clinical and Experimental Neuropsychology, 34* (6), 598-605.

Koekkoek, P.S., **Ruis, C.**, van den Donk, M., Biessels, G.J., Gorter, K.J., Kappelle, L.J., & Rutten, G.E.H.M. (2012). Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes- The ADDITION-Netherlands study: a cluster-randomized trial. *Journal of the Neurological Sciences, 314*, 71-77.

Ruis, C., & van Stralen, H.E. (2010). Neuropsychologisch profiel van twee volwassen patiënten met Tubereuze Sclerose Complex (TSC). *Tijdschrift voor Neuropsychologie*, *5* (1), 48-55.

Reijmer, Y.D., van den Berg, E., **Ruis, C.**, Kappelle, L.J., & Biessels, G.J. (2010). Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metabolism Research and Reviews, 26* (7), 507-519.

Ruis, C., Biessels, G.J., Gorter, K.J., van den Donk, M., Kappelle, L.J., & Rutten, G.E.H.M. (2009). Cognition in the early stage of type 2 diabetes. *Diabetes Care, 32* (7), 1261-1265.

Van den Berg, E., Nys, G.M.S., Brands, A.M.A., **Ruis, C.**, van Zandvoort, M.J.E., & Kessels, R.P.C. (2009). The Brixton Spatial Anticipation Test as a test for executive functions: Validity in patient groups and norms for older adults. *Journal of the International Neuropsychological Society, 15* (5), 695-703.

Anema, H.A., Wolswijk, V.W.J., **Ruis, C.**, & Dijkerman, H.C. (2008). Grasping Weber's illusion: The effect of receptor density differences on grasping and matching. *Cognitive Neuropsychology*, *25*, 951-967.

Nijboer, T.C.W., **Ruis, C.**, van der Worp, H.B., & de Haan, E.H.F. (2008). The role of 'Functionswandel' in metamorphopsia. *Journal of Neuropsychology, 2,* 287-300.

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

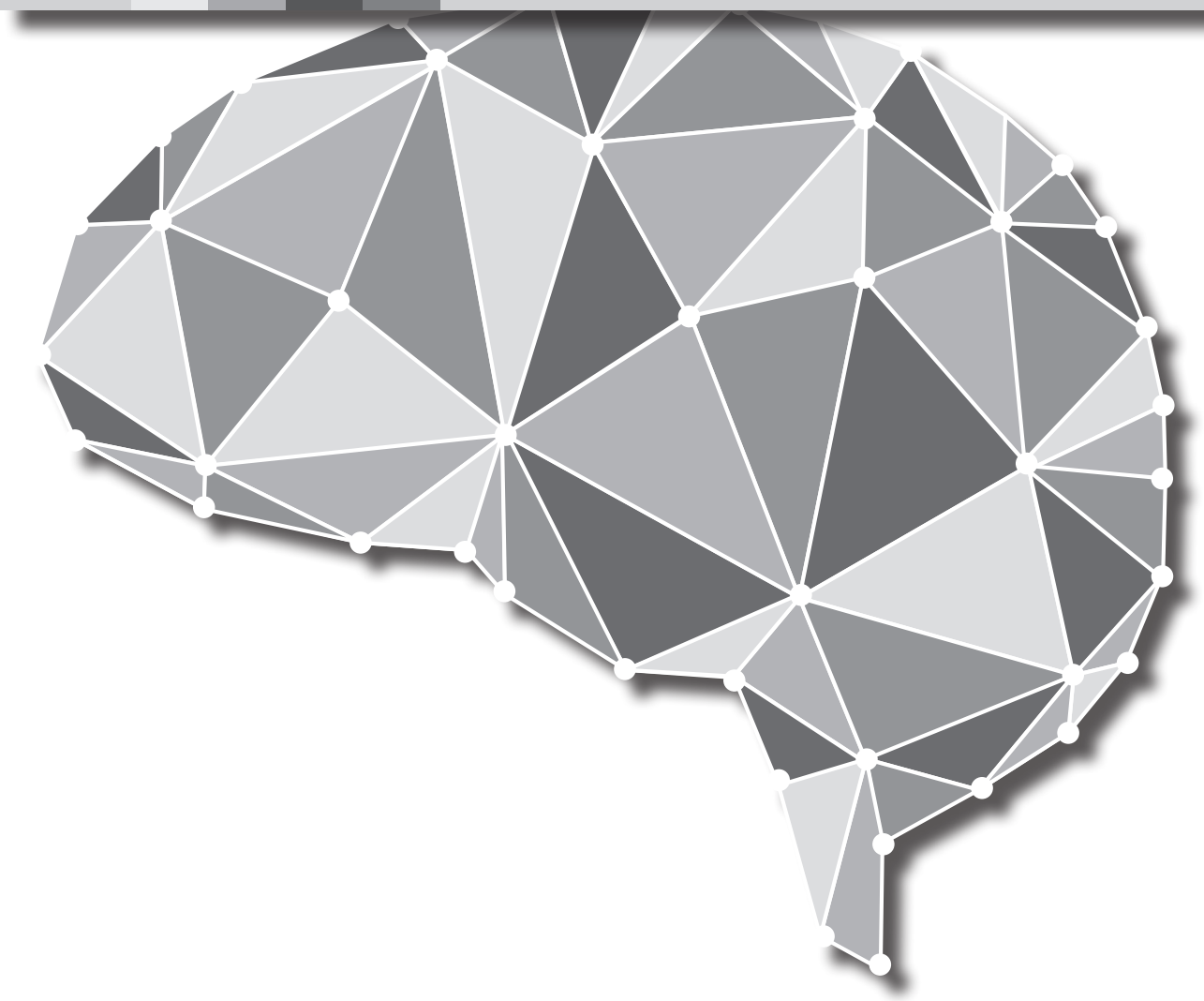
Kessels, R.P.C., **Ruis, C.**, & Kappelle, L.J. (2007). The impact of self-reported depressieve symptoms on memory function in neurological outpatients. *Clinical Neurology and Neurosurgery, 109* (4), 323-326.

Ruis, C., & Kessels, R.P.C. (2005). Effects of errorless and errorful face-name associative learning in moderate to severe dementia. *Aging Clinical and Experimental Research, 17* (6), 514-517.

Manuscripts submitted

Ruis, C., Huenges Wajer, I.M.C., Robe, P.A.J.T., & van Zandvoort, M.J.E. Awake craniotomy and coaching. *Submitted.*

Dankwoord



Dit proefschrift zou niet compleet zijn zonder een dankwoord. Schrijven is een proces. Een proces waarbij input van anderen heel belangrijk is, motiverende woorden wonderen kunnen doen, afleiding onmisbaar blijkt te zijn, en je de steun van je naasten hard nodig hebt. Mijn dank is dan ook groot voor allen die bij dit proefschrift betrokken waren.

Op de eerste plaats wil ik alle patiënten die ik de afgelopen jaren in het Universitair Medisch Centrum Utrecht gezien heb noemen. Zonder hen zou dit proefschrift niet tot stand zijn gekomen en ik wil hen bedanken voor hun vertrouwen in mij. Speciale dank gaat uit naar G.K. en F.V.

Mijn promotoren prof. Postma, prof. Kappelle en prof. Biessels en mijn co-promotor dr. van Zandvoort verdienen eveneens veel dank. Albert, jij creëerde mogelijkheden, gaf me veel vrijheid en had altijd vertrouwen in me. Jij hebt het initiatief genomen voor deze 'sprokkelroute' en daar ben ik je heel dankbaar voor. Jaap, jouw deskundigheid in het meesturen van mijn projecten hielp mij keer op keer verder. Je kritisch meedenken heeft mij veel geleerd. Geert Jan, jouw zeer kundige en punctuele begeleiding heb ik enorm gewaardeerd. Stukken werden altijd in rap tempo door jou gelezen en voorzien van commentaar. Heel fijn dat je altijd zo betrokken bent! Martine, al mijn hele carrière werk ik met jou samen en we delen onze passie voor de klinische neuropsychologie. Bedankt voor alles wat ik in de afgelopen jaren van je geleerd heb en de kansen die ik van je heb gekregen!

Prof. Kessels, beste Roy, bij jou zette ik mijn eerste stappen op onderzoeksgebied. Jij begeleidde mijn thesisonderzoek en dat leidde tot een mooie publicatie welke nu ook een hoofdstuk in dit proefschrift vormt. Een betere start wat betreft wetenschappelijk onderzoek had ik me niet kunnen wensen!

Prof. Dijkerman, beste Chris, ook bij jou deed ik in mijn masterjaar onderzoek. De jaren daarna volgde een mooie samenwerking, zowel bij Psychologische Functieleer als binnen het ziekenhuis. Fijn dat we elkaar zowel in onderwijs, onderzoek als kliniek tegenkomen.

Prof. de Haan, beste Edward, onder jouw verantwoordelijk startte ik mijn carrière in de kliniek. Dank voor deze kans en het vertrouwen dat je me gaf.

De ADDITION groep, en bovenal prof. Rutten, bedankt voor de kansen die ik bij jullie kreeg om ervaring op te doen met onderzoek.

Collega's van de afdeling Neurologie van het UMCU, en in het bijzonder collega's van de geheugenpoli, bedankt voor de prettige samenwerking. Rinie, Pierre, Kim en Willem, het was heel plezierig om samen met jullie mijn studies op te schrijven.

Collega's van de afdeling Neurochirurgie van het UMCU, Pierre en Marike, wat heb ik veel van jullie geleerd de afgelopen jaren tijdens de wakkere hersenoperaties. Het is een eer om deel uit te mogen maken van jullie team.

Neurostaf van de vakgroep Psychologische Functieleer, Albert, Chris, Martine, Tanja, Ineke, Esther en Stefan, wat fijn dat ik zo af en toe mijn werk aan jullie kon presteren en input voor verbetering ontving.

Collega's van de universiteit, bedankt voor jullie betrokkenheid en de koffiemomenten tussen het werk door. Helen en Tanja, tijdens jullie promotietraject heb ik met jullie beiden meegeschreven aan een artikel. We delen ons enthousiasme voor de kliniek en voor bijzondere casuïstiek! Josje en Rick, wat is het fijn om samen met jullie het neuropsychologie-onderwijs te mogen verzorgen! Ineke, bedankt dat je me hebt ingewijd in virtueel Tübingen. Ik ben trots op onze casusbeschrijving.

Collega's van de neuropsychologiegroep van het UMCU, Martine, Esther, Irene, Kim en Marieke, wat is het fijn om collega's te hebben die net zo enthousiast worden van de neuropsychologie als ik! Jullie betrokkenheid bij vakinhoudelijke zaken maar ook bij mijn privéleven is fantastisch en maken dat ik elke dag met plezier naar Utrecht ga.
Irene, wat heerlijk dat wij samen in een enthousiaste bui een nieuw project op kunnen zetten. Dank voor onze samenwerking!

Mijn paranimfen, wat ben ik blij dat jullie achter mij staan! Esther, wat fijn dat wij onze ambities en gedrevenheid kunnen delen. Al zeven jaar werken we zowel in het ziekenhuis als op de universiteit samen en ik kan me geen fijnere collega wensen! Haike, wat is het heerlijk om af en toe onder het genot van koffie bij te kletsen en te lachen. Ook al werken we niet meer op dezelfde afdeling en delen we onze kamer niet meer, het voelt nog wel zo!!

Naast het schrijven moet er ook tijd zijn voor ontspanning en wat zijn vrienden dan belangrijk! José en Kim, wat ben ik blij met onze onvoorwaardelijke vriendschap. Fijn dat jullie voor de broodnodige afleiding zorgen! Chantal, onze koffiemomentjes tussendoor zijn heerlijk, goed dat we elkaar altijd weten te vinden. Jaap en Co, bedankt voor alle gezellige momenten, inmiddels samen met Jaap junior! Ook Klaas, Gerben, Gert-Jan en Roderick die hebben rondgewandeld in virtueel Tübingen verdienen lof.

Lieve familie, dank voor jullie oprechte interesse in mijn werk. En dank voor alle gezellige momenten samen.

Gerrit en Adrie, fijn dat jullie altijd zo betrokken zijn en bedankt voor alle oppasmomenten. Zonder dat zouden wij niet zo'n carrière kunnen maken.

Lieve oma's, wat bijzonder dat ik jullie mijn boekje kan overhandigen. Lieve opa Schoemans, wat jammer dat je dit niet meer kan meemaken, je was tot op het allerlaatste moment zo betrokken en had graag naar de verdediging willen komen. Lieve opa Ruis, jij bent de aanleiding voor dit alles geweest. De spreuk voorin dit proefschrift hing bij jou in de werkplaats en maakte als klein meisje al indruk op me. Dank voor de inspiratie.

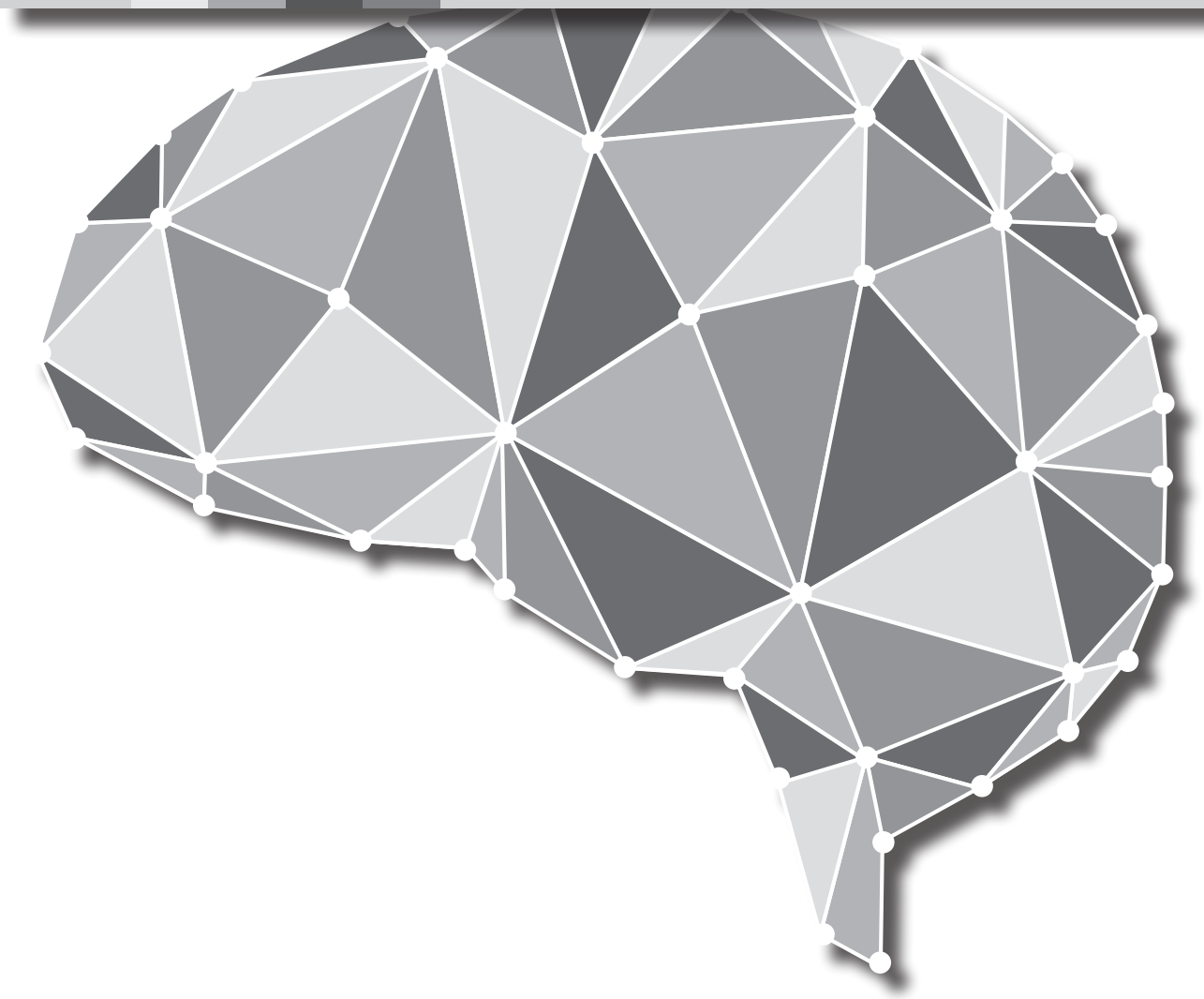
Gert-Jan en Arjan, wat fijn dat jullie mijn broers zijn. We hebben alle drie voor een geheel andere carrière gekozen, maar dat doet niets af aan de interesse voor elkaars werk. Gert-Jan, fijn dat je controle proefpersoon wilde zijn voor één van mijn studies en mijn stukken na wilde lezen. Arjan, bedankt voor alle momenten dat ik er niet uitkwam met statistiek en ik jou in de avonduren kon bellen.

Lieve papa en mama, jullie onvoorwaardelijke vertrouwen in mij hebben er voor gezorgd dat ik zo ver gekomen ben. Jullie denken in mogelijkheden en staan mij bij daar waar het nodig is. Mijn dank daarvoor is groot!

Lieve Harold, als je ons tien jaar geleden gezegd zou hebben dat we allebei zouden gaan promoveren hadden we dat denk ik niet geloofd. En nu verdedigen we twee maanden na elkaar ons proefschrift. Het balletje rolt soms anders dan je denkt, maar wat een mooie richtingen gaat het op. Jouw nuchtere kijk op zaken en je positieve instelling had ik de afgelopen periode soms hard nodig. Dank dat je er altijd voor me bent. Jouw liefde maakt mijn leven mooier, bij jou kom ik letterlijk en figuurlijk thuis.

En tenslotte mijn grote jongens Thijs en Jurre en mijn kleine meisje Julie. Jullie zijn mijn grote trots en maken alles relatief. Dank voor jullie liefde. Als jullie gelukkig zijn ben ik dat ook.

Curriculum Vitae



Carla Ruis is geboren op 1 december 1980 te Gorinchem. Na het afronden van haar VWO in 1999 aan het Altena College in Sleeuwijk ging zij psychologie studeren in Leiden. Tijdens haar studie liep zij stage bij het Leids Universitair Medisch Centrum alwaar haar interesse voor de neuropsychologie werd gewekt. Na het afronden van haar studie besloot Carla haar kennis te verdiepen middels de master Neuropsychologie in Utrecht. Tijdens deze master deed zij onder andere onderzoek bij Roy Kessels en Chris Dijkerman. In 2005 ging Carla werken bij de afdeling Neuropsychologie van het Universitair Medisch Centrum Utrecht. Onder supervisie van Martine van Zandvoort volgde zij de opleiding tot Gezondheidzorgpsycholoog. Zowel de algemene poli van de Neurologie als de geheugenpoli behoren tot haar werkzaamheden, en daarnaast is zij intensief betrokken bij de wakkere hersenchirurgie. Sinds 2009 is Carla tevens werkzaam als universitair docent bij de vakgroep Psychologische Functieleer van de Universiteit Utrecht. In 2014 is Carla gestart met de specialistenopleiding tot Klinisch Neuropsycholoog.

Carla Ruis was born on the first of December 1980 in Gorinchem. After finishing her secondary school in 1999 at the Altena College in Sleeuwijk she studied psychology at Leiden University. During her study she followed an internship at the Leiden University Medical Centre, where her interest in neuropsychology developed. After graduating in Leiden, Carla decided to deepen her knowledge with a master Neuropsychology in Utrecht. During her master she participated in research of Roy Kessels and Chris Dijkerman. Since 2005 Carla has been working at the Neuropsychology group of the University Medical Centre Utrecht. Under supervision of Martine van Zandvoort she was trained to become a certified psychologist. The neurological outpatient clinic and the memory clinic are important aspects of her work. Besides that, she is involved in awake craniotomies. Since 2009 Carla is also working as a lecturer at the department of Experimental Psychology of Utrecht University. In 2014 Carla started the training programme to become a certified clinical neuropsychologist.