Neuropsychology from paper-and-pencil to technology
Advancing cognitive rehabilitation

Lauriane Spreij

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Neuropsychology from paper-and-pencil to technology
Advancing cognitive rehabilitation

Van pen-en-papier naar technologie
Bekijk het door een andere bril

(met een samenvatting in het Nederlands)

Du papier-crayon à la technologie
Vue d'une autre approche

(avec un résumé en français)

Proefschrift

ter verkrijging van de graad van doctor aan de
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op dinsdag 24 november 2020 des middags te 2.30 uur

door

Lauriane Amandine Spreij

geboren op 27 januari 1990
te Morainvilliers, Frankrijk

Promotor: Prof.dr. J.M.A. Visser-Meily

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Contents

Prologue

The stories behind the numbers

In the world of scientific research, numbers are often the key. Numbers allow you to test hypotheses, make comparisons and predictions, and finally draw conclusions.

I want to tell you the stories behind the numbers. Who are the people who participated in this research who suffered from a stroke or a traumatic brain injury? In the end, it is all about these people. I asked several participants to tell their story.

This dissertation starts with the story of Tamara, a close friend since childhood.

I believe both healthcare professionals and researchers are inspired by individuals and their stories. Finding out about the stories behind the numbers may inspire you and help you understand, relate to, and look beyond the science. In addition, it might stress the importance of innovations with a true scientific basis.

The story of Tamara

On December 21st in 2015, someone lifted me up and accidentally hit my head against a traffic pole. I fell to the ground and heard others say: "she almost hit it", but I did. The next morning, I did not immediately realize what my condition was. Later that day, I had trouble staying awake. I went to the general practitioner who advised me to take some rest.

In the first weeks I suffered from headaches and extreme fatigue, so I slept most of the day. I was forgetful, had difficulty concentrating and was overly sensitive to light and noise. I had to give up on most of my social life. Exercising, going to a concert or cinema was no longer possible. In April 2016, I tried to resume my work for a few hours a day. It was strenuous and did not go very well. It could not sit in front of a computer screen for long, it was challenging to stay focused, and my memory regularly let me down while interacting with clients. Nevertheless, I was soon given more responsibilities. My symptoms got worse and it was hard to admit that I could no longer function as before the accident.

On July 20th 2016, the general practitioner referred me to a neurologist and rehabilitation physician. They put into words what I was going through and told me I suffered from acquired brain injury (ABI). They advised me to quit my job and to start treatment. A neuropsychological assessment was conducted to assess my cognitive functions with paper-and-pencil tests. Much effort was required to complete the tests. However, the tests only detected subtle shortages. What should have been a relief, was rather frustrating because my daily difficulties were not acknowledged. The test results had consequences later on. Since no clear cognitive impairment was detected, the occupational physician, for example, was not immediately willing to allow a slow reintegration which the rehabilitation physician had recommended.

It is now five years later and my recovery was a major challenge. Over the past year, several people with ABI contacted me because they also encountered a lack of understanding. There is still much to gain in terms of assessment, guidance and treatment for patients with ABI.

Chapter 1

General introduction

The story of Tamara is one that is frequently heard in clinical practice. Our current assessment tools sometimes fail to capture mild cognitive impairment. It is, however, of utmost importance that neuropsychological tests are sensitive enough to assess mild cognitive impairment, also because a treatment plan is formulated based on the test results. In addition, test results do not translate easily to daily life, which makes it challenging for neuropsychologists to make recommendations concerning daily life. The recommendations have, however, far-reaching consequences for a patient's live.

Neuropsychology

Neuropsychology is dedicated to understand the relation between the brain and neuropsychological functions, including emotion, behaviour and cognition. Cognition is an overall term for several different mental processes by which an individual acquires, processes, stores and interacts with information from the environment. Cognition is typically conceptualized in terms of domains of functioning, such as memory, attention, and executive functioning (Harvey, 2019).

Neuropsychologists work in a variety of institutions, including hospitals, rehabilitation centres, nursing homes, forensic organisations and research institutions. Within healthcare, clinical neuropsychologists are consulted whenever patients report complaints involving cognition. For instance, when patients experience difficulties regarding memory or attention. Clinical neuropsychologists are involved in the assessment, diagnosis, treatment and rehabilitation of patients across the life span with neurological, psychiatric and developmental conditions. The historical purpose of clinical neuropsychology was to assist in the diagnosis and localization of brain pathology by administering neuropsychological tests (Kibby, Schmitter-Edgecombe, & Long, 1998; Long, 1996). The role of neuropsychological testing has changed with the development of brain-imaging techniques that now allow clinicians to gather more precise information about the localization and type of brain pathology in much less time (Bilder, 2011; Long, 1996). Although clinical neuropsychologists continue to play a crucial role in the diagnosis of neurological conditions, there has been a changing focus in clinical neuropsychology. The focus of assessment has been moving away from diagnostic questions to questions about cognitive strengths and weaknesses and the impact of cognitive impairment on a patient's everyday functioning, such as the ability to work or to live independently (Heinrichs, 1990; Long & Kibby, 1995; Wilson, 1993). This is especially the case in a rehabilitation setting, where the diagnosis is already obtained.

In this dissertation, I focussed on clinical neuropsychology in a rehabilitation setting. Although clinical neuropsychologists focus on several areas during rehabilitation (e.g.,

emotion, behaviour), I primarily focussed on cognition. Cognitive rehabilitation starts with a thorough neuropsychological assessment to identify cognitive strengths and weaknesses. The conclusions of the assessment are used to formulate an appropriate treatment plan. In this dissertation, we included patients with acquired brain injury (ABI), which is the largest population in rehabilitation medicine in the Netherlands (Revalidatie Nederland, 2017).

Acquired Brain Injury

ABI is defined as brain damage that occurs after birth, and is caused by either traumatic brain injury (e.g., head trauma due to a traffic accident or assault) or nontraumatic injury derived from either an internal or external source (e.g., ischemic or haemorrhagic stroke, brain tumours, infection, poisoning or substance abuse). In the Netherlands, there were 645,900 patients registered with the diagnosis ABI in 2016 (Rijksinstituut voor Volksgezondheid en Milieu, 2017). The most common causes of ABI are ischemic or haemorrhagic stroke and traumatic brain injury (TBI). There are approximately 40,000 stroke patients and 20,000 TBI patients admitted to the hospital each year (de Boer, van Dis, Visseren, Vaartjes, & Bots, 2018; Hersenstichting Nederland, 2015). However, because a majority of TBI patients are not admitted to hospitals, the true incidence of TBI is estimated to be 85,000 patients per year.

Depending on the location and severity of the brain injury, ABI can result in physical, social, emotional, behavioural and cognitive impairment, and outcome can range from complete recovery to permanent disability. Cognitive impairment can be one of the most devastating consequences of brain injury, as it generally interferes with activities of daily living (e.g., eating, bathing, getting dressed), relationships, leisure and work. Previous research showed that cognitive impairment may negatively affect functional independence (Rabinowitz & Levin, 2014; Zinn et al., 2004) and participation in society (Ezekiel et al., 2019; Jette, Keysor, Coster, Ni, & Haley, 2005; Mole & Demeyere, 2020), such as return to work (Donker-Cools, Schouten, Wind, & Frings-Dresen, 2018; van der Kemp et al., 2019). Moreover, cognitive impairment may lead to significant burden upon the families of patients (Pollock, St George, Fenton, & Firkins, 2014; Ponsford, Olver, Ponsford, & Nelms, 2003).

Cognitive rehabilitation

Patients with ABI are referred for cognitive rehabilitation, when patients report cognitive complaints and/or cognitive impairment is detected with a screening instrument. When a multidisciplinary approach is essential, patients are referred to either outpatient rehabilitation

care or inpatient rehabilitation care. Cognitive rehabilitation generally involves a multidisciplinary team including rehabilitation physicians, occupational therapists, speech therapists, social workers and neuropsychologists. The overarching aim of cognitive rehabilitation is to promote functional independence and participation in society by improving cognitive functioning (Cicerone et al., 2000; Nederlandse Vereniging van Revalidatieartsen, 2015; Tsaousides & Gordon, 2009). Cognitive rehabilitation starts with a thorough neuropsychological assessment that is conducted by a clinical neuropsychologist to identify cognitive strengths and weaknesses. The conclusions of the assessment are used to formulate an appropriate treatment plan. See Figure 1.1 for the clinical pathway of cognitive rehabilitation.

Clinical interview

As first step, a clinical interview is conducted to gather information from the patient and a relative (or significant other) about important aspects of the history, lifestyle and symptoms. An important aspect is the inventory of cognitive complaints a patient and relative report. Discrepancies between patients' and relatives' reports are very informative. This information may reflect a patient's self-awareness of the difficulties that occur in daily life (Hochstenbach, Prigatano, & Mulder, 2005; Vakil, 2012).

Neuropsychological testing

A neuropsychological test battery mostly consists of paper-and-pencil tests, with each test targeting a specific cognitive domain (Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006). The interpretation of neuropsychological tests is based on the central assumption that the test performance represents the best effort of the patient. The goal of testing is therefore to always obtain the best performance the patient is capable of producing (Lezak et al., 2012). Clinical neuropsychologists elicit the best performance of patients by providing optimal conditions. For instance, neuropsychological testing should be undertaken in a quiet room with sufficient light, with no foot traffic or distracting views.

Analysis and integration of findings

Performances on neuropsychological tests are generally scored by examining a final score, such as the time required to complete a test, the number of correct responses, or the number of correctly placed elements of a final drawing. The scores of a patient are compared with the test scores of a reference group with the same age, sex, and educational attainment. This comparison allows for the determination whether a patient is performing as would be expected, giving its age, sex and educational attainment, or is performing poorer or better than expected. Based on the results, a cognitive profile can be generated defining cognitive

strengths and weaknesses. The cognitive profile is integrated with information gained from the medical files, the clinical interview, and behavioral observations. The findings are described in a neuropsychological report including recommendations derived from the assessment with regard to treatment.

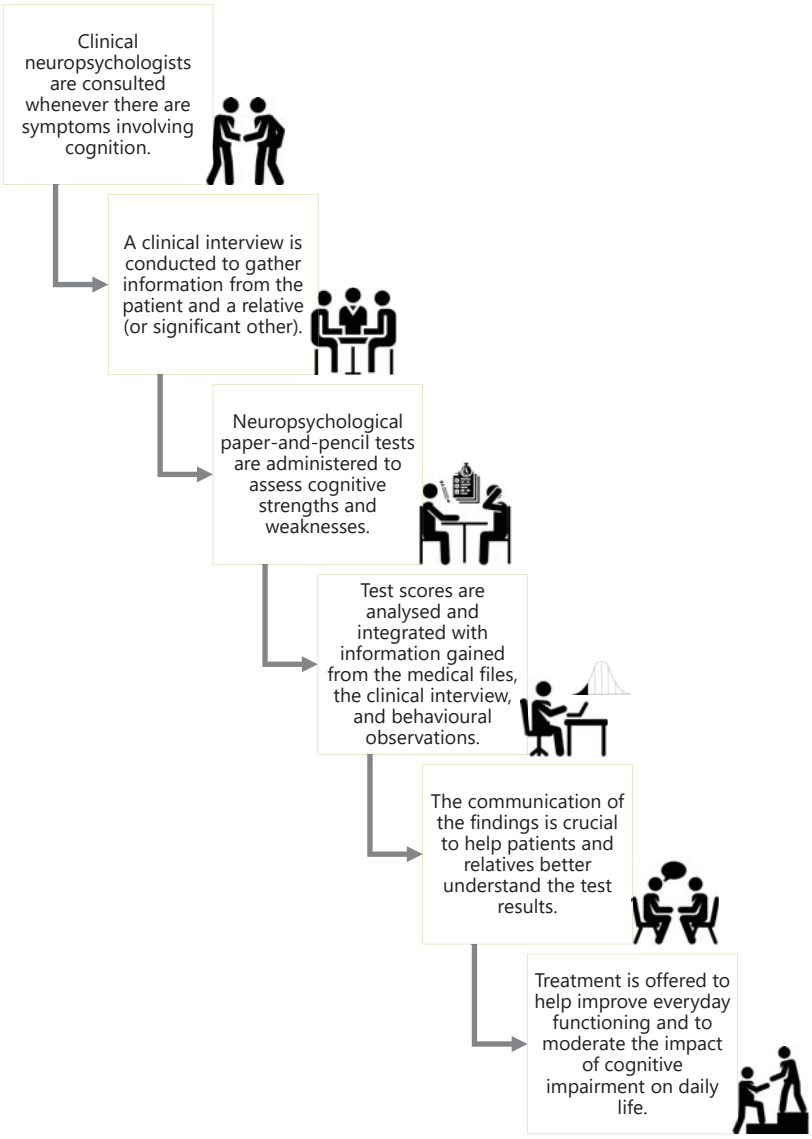

Figure 1.1. A visualisation of the clinical pathway of cognitive rehabilitation for a patient with acquired brain injury (ABI). The clinical pathway consists of a clinical interview to gather relevant information, neuropsychological testing, analysis and integration of findings, feedback to the patient and relative, and treatment.

Communication of the findings

The communication of neuropsychological findings is crucial to help patients and relatives understand the test results and their implications in daily life. A clinical neuropsychologist plays a central role in psycho-education, by providing the information in understandable terms within an emotionally supportive context. The goal is to help patients understand the nature of their difficulties and to assist patients in decision-making concerning the recommendations derived from the assessment with regard to treatment (Rosado et al., 2018). If patients decide to start treatment, the communication of the findings to the multidisciplinary team is essential to formulate treatment goals.

Treatment

Treatment is offered to help improve everyday functioning and to diminish the impact of cognitive impairment on daily life. Rehabilitation approaches are thought to be best employed in a multidisciplinary manner so that all involved clinicians are actively engaged in the treatment. Treatment may consist of retraining skills, teaching compensatory strategies, making environmental modifications to a patient's home or workplace, and improving a patient's awareness and acceptance of his/her disabilities (Cicerone et al., 2000).

Limitations and implications for research

Clinical interview

An important aspect of a clinical interview is the inventory of cognitive complaints. Cognitive complaints are defined as the subjective difficulties patients encounter in daily life (Van Rijsbergen, Mark, De Kort, & Sitskoorn, 2014). To date, however, there is little standardization in the assessment of cognitive complaints, which may lead to the possibility that complaints are overlooked, or that an increase or improvement of complaints remains unnoticed. Several questionnaires are available to assess cognitive complaints (e.g., Checklist for Emotional and Cognitive Consequences), yet the items are not related to daily life activities. Items without a daily life example are often considered abstract and challenging for patients. In **Chapter 2**, we developed an inventory for patients with ABI to systematically assess cognitive complaints across several cognitive domains and several daily life activities. As discrepancies between patients' and relatives' reports are of great diagnostic value, we additionally developed a version for relatives.

Neuropsychological tests

Neuropsychological paper-and-pencil tests are not always sensitive enough to detect mild cognitive impairment. It is, however, of utmost importance that neuropsychological tests are sensitive to mild cognitive impairment. Research has focused on embracing technological advances in neuropsychological assessment (Parsons, 2016). Digital test batteries have been developed to administer, score, and interpret measures of cognitive function (Kane & Kay, 1992; Parsey & Schmitter-Edgecombe, 2013; Rabin et al., 2014; Schlegel & Gilliland, 2007). Digital tests have important benefits compared to paper-and-pencil tests, as they allow a more standardized administration and an automatized scoring (Bauer et al., 2012; Cernich, Brennana, Barker, & Bleiberg, 2007). The most important benefit is that digital tests open the opportunity to develop novel outcome measures to assess more subtle cognitive impairment (Parsey & Schmitter-Edgecombe, 2013). Due to a continuous data collection, digital tests have the potential to assess cognitive processes that might not be observed or objectified with paper-and-pencil tests. However, as illustrated in the story of Tamara, patients with ABI may be sensitive to light, which may hamper the use of technological devices. In **Chapter 3**, we first investigated the feasibility and applicability of digital neuropsychological assessment in patients with ABI. In **Chapter 4**, we capitalized the opportunities afforded by digital tests and developed novel outcome measures to assess more subtle cognitive impairment. We assessed performance stability by evaluating the number of fluctuations in test performance.

Complementary tests

Test results on neuropsychological paper-and-pencil tests do not translate easily to daily life. Previous research has reported a lack of ecological validity, suggesting that test performances do not predict daily life performances very well (Chaytor & Schmitter-Edgecombe, 2003). The lack of ecological validity may be explained by the fact that neuropsychological tests target one cognitive function at the time (e.g., memory), whereas daily life activities require multiple cognitive functions at once (e.g., cooking). Also, neuropsychological tests are administered in a quiet and non-distracting room, whereas daily life situations are often complex and dynamic (e.g., traffic, open workspace).

A high ecological validity is important since the recommendations based on the test results may have significant consequences for the lives of patients and their relatives (Chaytor & Schmitter-Edgecombe, 2003). Ecological-valid assessment has evolved as an area of focus within clinical neuropsychology (Chaytor & Schmitter-Edgecombe, 2003; Parsey & Schmitter-Edgecombe, 2013; Parsons, 2016; Rose, Brooks, & Rizzo, 2005; Spooner & Pachana, 2006). Complementary tests have been developed and used in clinical practice, such as observational scales or tests that are conducted in the real-world. Over the last

decade, Virtual Reality (VR) has shown promise to assess cognitive functioning in simulated environments resembling daily life (Larson, Feigon, Gagliardo, & Dvorkin, 2014; Parsons, 2015; Rose et al., 2005; Schultheis, Himelstein, & Rizzo, 2002; Shin & Kim, 2015). With VR, ecological-valid tests can be developed without losing control over stimulus presentation (Parsons, 2015; Rizzo, Schultheis, Kerns, & Mateer, 2004). In **Chapter 5**, we investigated the concepts of static tests (e.g., paper-and-pencil tests) and dynamic tests (e.g., ecological-valid tests) in the assessment of visuo-spatial neglect, a frequent and disabling disorder in lateralized attention following stroke. Furthermore, several user interfaces are available when using VR, namely non-immersive VR by using a computer monitor or projection screen and immersive VR by using a head-mounted display. In **Chapter 6**, we investigated a non-immersive VR-based task to assess visuo-spatial neglect following stroke. In **Chapter 7**, we investigated the feasibility of non-immersive and immersive VR in stroke patients referred for in- or outpatient rehabilitation care.

Treatment

Treatment has been primarily directed to train patients to use adaptive and compensatory strategies to improve everyday functioning (Cicerone et al., 2000). Current understanding of neuroplasticity has led to novel insights in treatment by applying a remediation approach. Neuroplasticity is the ability of the brain to create, strengthen, and modify neurological connections. It occurs at many levels from molecules to cortical reorganization. A wide range of treatments are developed based on the principles of neuroplasticity and are directed to restore or retrain cognitive function (van Heugten, Ponds, & Kessels, 2016). In **Chapter 8**, we provide an overview of studies characterizing the most discussed treatments applying a remediation approach in memory rehabilitation: VR-based training, computerized-based cognitive retraining and non-invasive brain stimulation.

Objectives of this dissertation

To summarize, the general objective of this dissertation was to investigate the use and added value of novel instruments in cognitive rehabilitation for patients with acquired brain injury (ABI). To achieve this objective, we formulated three aims: (1) to develop an instrument to systematically assess cognitive complaints in daily life; (2) to investigate the use of a digital version of existing tests to measure cognitive function, and to capitalize the opportunities afforded by digital tests by developing novel outcome measures; (3) to investigate the use and added value of advanced technology to assess cognitive function in a more sensitive and dynamic manner, and to inventory the use of technology to improve cognitive function.

A schematic outline of this dissertation is depicted in Figure 1.2. A general discussion is presented in **Chapter 9**. In this chapter, I attempt to integrate the findings of the individual studies, address methodological considerations, and formulate recommendations for future research and clinical practice.

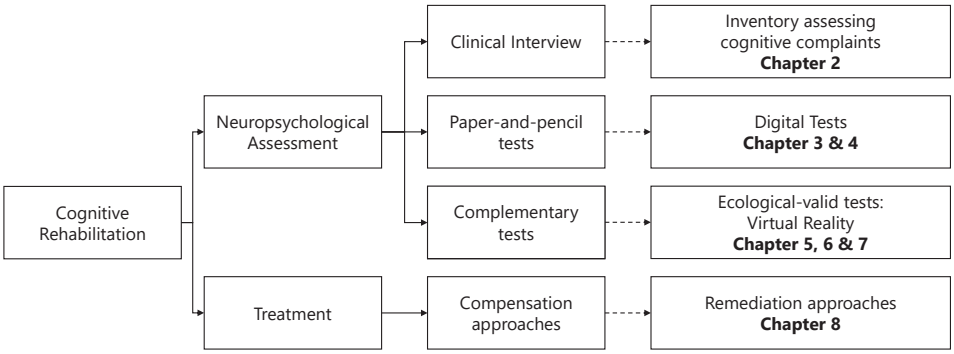

Figure 1.2. Schematic outline of this dissertation.

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Part I

Paper-and-pencil

In September 2011, I hit my head to such an extent that it caused brain damage. My general practitioner initially thought I had a concussion and advised me to take some rest. When it did not get better, I was referred to a neurologist and a brain scan was made. An MRI scan showed a blood clot, which caused pressure in my brain. I was operated by a neurosurgeon on May 21st, in 2012. After the surgery, little attention was paid to the consequences of the brain damage on daily life. I had a managing position in the police force, but I was no longer able to do my job. It was hard for me to pay attention to my work and I couldn't tolerate bright computer screens. I suffered from severe fatigue and I was oversensitive to noise and stress. I was no longer the person who I previously was and I felt completely lost. A colleague informed me about the possibilities of rehabilitation care. I contacted the department and they helped me immediately. It was a warm welcome and from that moment it started to get better. A social worker, psychologist, occupational therapist and a rehabilitation physician worked beautifully together and gave my difficulties a name: acquired brain injury. I felt relieved I was not alone. They gave me insight into my shortcomings and how to deal with them. Since the brain injury, I have headaches on a daily basis. I am no longer able to work, but I am at peace with it. I participated in research, because I want to help others. I don't want anyone to feel as lost as I felt. Because people don't notice anything different about me, I want to raise awareness. Research will take us further by developing new methods to give more insight into the consequences of acquired brain injury.

Chapter 2

Cognitive Complaints - Participation (CoCo-P): The development and clinical use of a novel inventory measuring cognitive complaints in daily life

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Neuropsychological Rehabilitation (2019), *2*, 1–23.

Abstract

Cognitive difficulties can be subtle and only come to light when patients return home from inpatient care and start to participate in society. Subjective cognitive complaints often interfere with participation, hence capturing cognitive complaints systematically is important. We developed a patient- and relative-reported measure to assess cognitive complaints during daily life activities across the memory, attention and executive domain for patients with acquired brain injury (ABI). The inventory *Cognitive Complaints - Participation* (CoCo-P) was created based on a literature review, consultations with experts, semi-structured interviews with patients, and a quantitative study. The inventory was administered to patients with ABI (n = 46), their relatives (n = 33) and healthy controls (n = 102) to finalize the inventory. We examined the reported complaints per daily life activity and cognitive domain of patients and healthy controls, and we compared the patients' and relatives' reports. The majority of patients (87–96%) experienced cognitive complaints, mostly related to attention, at work/education, during leisure activities, and in contact with family/friends and community. Patients reported more cognitive complaints than relatives. The CoCo-P seems appropriate to capture cognitive complaints in daily life in patients with mild ABI. Additional research is needed in terms of reliability and validity.

Introduction

Acquired brain injury (ABI), mostly caused by stroke or traumatic brain injury (TBI) (Cicerone et al., 2000), frequently results in impairments in memory (Das Nair & Lincoln, 2007; Spreij, Visser-Meily, Van Heugten, & Nijboer, 2014), attention (Virk, Williams, Brunsdon, Suh, & Morrow, 2015), and executive function (Chung, Pollock, Campbell, Durward, & Hagen, 2013; Cicerone, Levin, Malec, Stuss, & Whyte, 2006). Cognitive impairments can be subtle and often only come to light when patients return home from the hospital or rehabilitation centre and start to participate in society (e.g., work, travel). *Participation* refers to the engagement of a person in daily life activities in a social context (Viscogliosi, Desrosiers, Belleville, Caron, & Ska, 2011). The presence of cognitive impairment is strongly associated with restrictions in participation (Ezekiel et al., 2018; Jette, Keysor, Coster, Ni, & Haley, 2005; Mole & Demeyere, 2018; Viscogliosi et al., 2011) and is the greatest burden to patients and their families (Ponsford, Olver, Ponsford, & Nelms, 2003).

Assessment of cognitive impairments is mostly done with neuropsychological tests. These tests, however, often fail to objectify subtle disorders and to determine which daily life difficulties the patient is likely to encounter (Bielak, Hatt, & Diehl, 2017; Chaytor & Schmitter-Edgecombe, 2003). In addition, cognitive impairments are not necessarily an indication of cognitive complaints, and vice versa (Clarke, Genat, & Anderson, 2012; Duits, Munnecom, Van Heugten, & Van Oostenbrugge, 2008; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Rijsbergen, Mark, De Kort, & Sitskoorn, 2014). Cognitive complaints may also interfere with participation (Benedictus, Spikman, & Van Der Naalt, 2010; Robison et al., 2009; van der Naalt, van Zomeren, Sluiter, & Minderhoud, 1999); hence systematically capturing cognitive complaints is important (Rijsbergen et al., 2014).

However, suitable inventories that measure cognitive complaints during daily life activities are not available. Several instruments, like the Stroke Impact Scale (scale – memory and thinking) (Duncan, Wallace, Studenski, Lai, & Johnson, 2001), Cognitive Failure Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982), Brain Injury Complaint Questionnaire (Vallat-Azouvi et al., 2018), and the Checklist for Emotional and Cognitive Consequences (CLCE-24) (van Heugten, Rasquin, Winkens, Beusmans, & Verhey, 2007) are available to identify cognitive complaints, yet the items are not directly related to daily life activities. On the contrary, several instruments particularly focus on daily life activities in a social context (i.e., participation), such as the Frenchay Activities Index (Holbrook & Skilbeck, 1983), Instrumental Activities of Daily Living (Lawton & Brody, 1969), Assessment of Life Habits (Fougeyrollas & Noreau, 2002), and the Utrecht Scale for Evaluation of Rehabilitation

– Participation (USER-P) (Post et al., 2012), yet the focus is not on cognition as the reported restrictions may also be caused by motor, emotional and/or behavioural problems.

The primary aim of this study was to develop an inventory for patients with ABI to measure cognitive complaints across several cognitive domains as well as across several daily life activities. In a sequence of steps (Wiklund et al., 2016), an inventory suitable for patients with ABI was developed: (1) a literature search explored the availability of inventories measuring cognitive complaints on level of participation; (2) modifications were made to suit our target population after consulting an expert panel; (3) semi-structured interviews were held with patients ($n = 7$) to evaluate face validity (i.e., subjective evaluation whether the test seems to measure what it reports to measure); and (4) a quantitative study was conducted to finalize the inventory by administering the inventory in patients with ABI, their relatives and healthy controls. A secondary aim was to develop a version for relatives as impairment in self-awareness and the overestimation of cognitive abilities are common issues in ABI patients (Fischer, Trexler, & Gauggel, 2004; Kelley et al., 2014; Prigatano, Altman, & O'Brien, 1990; Sbordone, Seyranian, & Ruff, 1998). Based on the finalized inventory, we compared the reported complaints across daily life activities (e.g., work, travel), cognitive domains (i.e., memory, attention, executive function) and the level of fatigue between patients and healthy controls. Finally, we compared the patients' and relatives' reports regarding the cognitive complaints and the perceived level of fatigue.

Methods

Development of the Cognitive Complaints - Participation (CoCo-P)

Literature search and gap analysis

A literature search was conducted and identified multiple inventories measuring cognitive complaints and/or participation (See Appendix 2.1 for an overview). Only the Cognitive Impairment in Daily Life (CID) (Johansson, Marcusson, & Wressle, 2016) was considered to meet the criteria to measure cognitive complaints, across cognitive domains, directly related to several daily life activities. This inventory was, however, developed for patients with a neurodegenerative disorder, such as mild cognitive impairment and dementia. As ABI and neurodegenerative disorders significantly differ in pathology, demographics (e.g., age) and cognitive sequelae, we set out to develop a new inventory based on the structure of the CID.

Expert panel and revision

We arranged two meetings with an expert panel that consisted of healthcare professionals (rehabilitation physicians and occupational therapists). Based on their expertise, we aimed to select daily life activities (e.g., work, finances, driving) in which our target population (i.e., outpatients with ABI, living at home) frequently reports complaints. Also, the response options were adjusted and based on the USER-P (Post et al., 2012) and reflected different grades of independence and effort (0 [independent without effort], 1 [independent with effort], 2 [with help], 3 [not possible]). It included a fourth response option (4 [not applicable]), as some activities (e.g., driving a car, cooking) are not applicable for some patients. Emoticons were used in the response options, in addition of the written words, to denote the different points on the scales.

Next, we arranged two meetings with cognitive neuroscientists. Attention, memory and reasoning abilities (i.e., problem solving ability that requires both memory and executive functioning; Spielberger, 2004)) are the basic functions required to complete tasks and solve everyday problems (Bielak et al., 2017). We established on three cognitive models presenting memory (Squire, 1992, 2004), attention (Petersen & Posner, 1990, 2012; Posner & Rothbart, 2007) and executive function (Ylvisaker, Szekeres, & Feeney, 1998) to use as theoretical framework for the selection of the items. We selected items focusing on memory (i.e., retrospective memory, prospective memory), attention (i.e., arousal, orienting, monitoring, sustained) or executive function (i.e., planning, self-evaluating, initiative, flexibility) across each daily life activity. Language and visual-perceptual functions were not included in the inventory. Language disorders (e.g., aphasia) and lower-level visual disorders (e.g., scotoma, diplopia) are often prominent in daily life and relatively more easily recognized by clinicians and patients. Lower-level visual disorders are also frequently regarded as *pre*-cognition. In contrast, higher-order perceptual disorders (e.g., prosopagnosia, simultanagnosia) are more challenging to capture. Luckily, suitable inventories for both lower- and higher-level visual-perceptual disorders as well as language disorders are already available, such as the Cerebral Visual Disorders (CVD) (Kerkhoff, Schaub, & Zihl, 1990), the Screening Test for Cognitive Communication (STCC) (Paemeleire, 2014), and the Communicative Participation Item Bank (CPIB) (Baylor, Burns, Eadie, Britton, & Yorkston, 2011). Based on the expert meeting, a first draft was conducted.

Patient panel and revision

The draft version was administered in seven patients, and semi-structured interviews were conducted to evaluate face validity. See Table 2.1 for the demographic and clinical characteristics of these patients. Five patients were visited at home and two patients

performed the evaluation by e-mail. We asked patients whether any important daily life activities were missing. We included five questions that could be answered on a Visual Analogue Scale (VAS) ranging from 0–10: (1) How clear was the instruction?; (2) How clear were the items?; (3) How clear were the response options?; (4) How familiar were the daily life activities?; and (5) How do you evaluate the length of the inventory? Additional remarks were administered.

For each question, the mean VAS score was above 9, for the exception of one question (How clear were the items?) that had a mean score of 7.1. Based on their suggestions, we adjusted the formulation of several items. Also, the time frame was not clear, so we clarified that the items reflected the patients' *current* state (i.e., post ABI onset). The response options were appropriate and well understood by the patients.

Face validity was considered adequate as all patients considered the daily life activities relevant and the items representative for their difficulties. Three patients did feel emotional and behavioural changes were missing in the inventory. We considered their suggestion, however, we felt that including those topics was not in line with our main scope of the inventory (i.e., cognitive complaints post-ABI). Fatigue was also reported as a common complaint especially after consecutive activities, which is in line with previous research (Visser-Keizer, Hogenkamp, Westerhof-Evers, Egberink, & Spikman, 2015). Therefore, we included an item measuring fatigue after each daily life activity by using a VAS (range 0–10 cm). Patients are asked to indicate in what extend a daily life activity is tiring along a visual analogue line that extends between two extremes (i.e., "not tiring at all" to "extremely tiring").

Table 2.1. Demographic and clinical characteristics of the patients that were interviewed

	Patients (*n* = 7)
Male (n)	3
Age in years (median, range)	47.5 (28–55)
Level of education (n)	
Low	1
Moderate	0
High	6
Type of ABI (n)	
Stroke	3
TBI	2
Brain tumour resection	2
Time ABI onset (median, range)	33 months (21–54)

Abbreviations: Acquired Brain Injury (ABI); Traumatic Brain Injury (TBI).

Preliminary inventory used in quantitative study

A preliminary version of the inventory was developed based on the expert meetings and semi-structured interviews with patients. The patient-reported and relative-reported measures contained 42 items focusing on memory, attention or executive function over 11 daily life activities (i.e., work/education, leisure activities, travel, driving, finances, use of medication, family life, contact with family/friends, contact with community, cooking, grocery shopping). After each activity the level of fatigue was measured using a VAS. See Table 2.2 for an overview of the preliminary version that was used in the quantitative study.

Quantitative study

Participants

Patients with ABI, their relatives and healthy controls were asked to participate. We recruited patients with ABI who received outpatient rehabilitation in either the *University Medical Centre Utrecht* or *De Hoogstraat Rehabilitation Centre*, the Netherlands. Patients had to meet the following inclusion criteria: 1) aged between 18–80 years old; and 2) fluent in Dutch. Patients were asked if a close relative was willing to participate. Furthermore, the healthy controls had to meet the following inclusion criteria: 1) aged between 18–80 years old; 2) fluent in Dutch, and 3) no history of neurological and/or psychiatric disorders. Healthy controls were recruited among acquaintances of the researchers and by using advertisements in online newsletters and websites. All participants gave written informed consent. The experiment was performed in accordance with the Declaration of Helsinki. The research protocol was approved by the Medical Ethics Committee of the University Medical Centre (METC protocol number 17-407/C).

Procedure

Patients (and relatives) were invited by a rehabilitation physician or a neuropsychologist to participate. After confirmation, the CoCo-P along with the informed consent form was sent by post. Patients were instructed to bring the completed forms to a scheduled appointment or return them by post. Healthy controls returned the completed forms by post.

Finalizing the inventory based on the data of the quantitative study

To finalize the inventory, we revised the response distributions of each item within healthy controls and patients (See Appendices 2.2 and 2.3). The response options (four-point scale) were dichotomized into "no complaints" (i.e., [0] independent, without effort) and "complaints" (i.e., [1] independent, with effort, [2] with help or [3] not possible). The presence

Table 2.2. Preliminary version used in the quantitative study: overview of the items for each daily life activity across the cognitive (sub)domains

Daily life activity	Items	Cognitive domain
Work/education	1) Planning activities for the day/week	EF Planning
	2) Paying attention to my work	A Sustained
	3) Performing my activities in busy surroundings	A Monitoring
	4) Tolerating bright displays	A Monitoring
	5) Performing activities without extra breaks	A Sustained
	6) Remembering information	M Retrospective
	7) Checking my work	EF Self-evaluating
	Fatigue	
Leisure activities	8) Staying awake during activities	A Arousal
	9) Doing several activities consecutively	A Sustained
	10) Performing leisure activities	EF Initiative
	11) Remembering related people	M Retrospective
	Fatigue	
Travel	12) Planning a journey	EF Planning
	13) Adjusting the plan	EF Flexibility
	14) Remembering the arrival/departure time*	M Prospective
	Fatigue	
Driving	15) Paying attention to other road users	A Orienting
	16) Staying awake while driving	A Arousal
	17) Remembering unfamiliar routes*	M Retrospective
	18) Maintaining the appropriate speed	EF Self-evaluating
	Fatigue	
Finances	19) Planning my budget and spending	EF Planning
	20) Paying the bills on time	EF Initiative
	Fatigue	
Use of medication	21) Planning new prescription	EF Planning
	22) Remembering taking my medication	M Prospective
	23) Taking my medication*	EF Initiative
	24) Intake of medication at fixed times	EF Planning
	Fatigue	
Family life	25) Organizing activities for my family	EF Initiative
	26) Remembering events or conversations	M Retrospective
	27) Participating in family life	EF Initiative
	Fatigue	
Contact with family/friends	28) Conversing in busy surroundings	A Orienting
	29) Maintaining social events without extra breaks	A Sustained
	30) Remembering names of family members/friends	M Retrospective
	31) Maintaining contact with family/friends	EF Initiative
	Fatigue	
Contact with community	32) Remembering names of people I just met*	M Retrospective
	33) Making appointments	EF Initiative
	Fatigue	

Table 2.2 continues on next page.

Table 2.2. *Continued*

Daily life activity	Items	Cognitive domain
Cooking	34) Checking ingredients before cooking 35) Paying attention to cooking 36) Remembering the order 37) Maintaining the right temperature 38) Accurately estimating the time 39) Multitasking while cooking *Fatigue*	EF Planning A Sustained M Retrospective EF Self-evaluating EF Planning EF Flexibility
Grocery shopping	40) Planning the needed products 41) Remembering the products 42) Finding the products *Fatigue*	EF Planning M Prospective EF Planning

Abbreviations: memory (M); attention (A); executive function (EF). * These items were excluded from the final inventory (See "Finalizing the inventory based on data of the quantitative study").

of floor or ceiling effects were important determinants. Items were deleted from the final version and further analyses when: (1) > 20% of healthy controls reported "complaints" on the item in question (which means the item can be considered "quite challenging", even for healthy controls); and (2) < 10% patients reported "complaints" on the item in question (which means the item can be considered "not challenging enough"). More than 20% of the healthy controls reported complaints on item 14 (i.e., remembering the time of arrival and departure), 17 (i.e., remembering unfamiliar routes), and 32 (i.e., remembering names of people I just met). These items were excluded as they were not suitable in differentiating between patients with ABI and healthy controls. Regarding item 14 and 17, this finding might be explained by the fact that nowadays technology (e.g., application on phone, navigational system) is used during these activities. So performing these activities on its own merits might be considered challenging. The exclusion of item 32 caused the daily life activity "contact with community" to contain only one item (i.e., item 33). For this reason, item 33 was added to "contact with family/friends", and the daily life activity was renamed into "contact with family/friends and community". Only two patients (< 10%) reported complaints on item 23 (i.e., taking my medication). Due to the lack of variance, this item was excluded from the final inventory and further analyses.

The daily life activity "use of medication" (i.e., items 21 [planning prescription refill]; item 22 [remembering taking my medications]; item 24 [intake of medication at fixed times]) seemed not applicable in our patient population. However, we did not exclude this activity from our inventory because 20–33% of the patient that used medication did report complaints on these items.

As a result of a review of available literature, expert meetings with health professionals and cognitive neuroscientists, semi-structured interviews with patients, and a quantitative study, the final version of the inventory was developed. The *Cognitive Complaints - Participation* (CoCo-P) is a patient-reported and/or relative-reported measure that contains 38 items focusing on memory, attention or executive function over 10 daily life activities (i.e., work/education, leisure activities, travel, driving, finances, use of medication, family life, contact with family/friends and community, cooking, grocery shopping). An English translation of the inventory is presented in Appendix 2.4. Note that the results in this study are obtained with the original Dutch version.

Statistical analyses on data of the quantitative study with the final inventory

Demographic and clinical characteristics

We collected data on sex, age and level of education. Level of education was assessed using a Dutch classification system (Verhage, 1965), that consists of 7 levels, with 1 being the lowest (less than primary school) and 7 being the highest (academic degree). These levels were converted into three categories for analysis: low (Verhage 1–4), average (Verhage 5), and high (Verhage 6–7). Non-parametric tests (Kruskal-Wallis non-parametric ANOVA and Chi-square test for categorical variables) were used to compare demographic characteristics between the patients and healthy controls. Additionally, we extracted the following characteristics from the medical files: ABI type (i.e., stroke, TBI, brain tumour resection), time since ABI onset, lesion side, and the current state regarding work employment. If a neuropsychological assessment was scheduled within three months around the administration of the inventory, we collected the patient's neuropsychological performance on four tests (i.e., Mini-Mental State Examination – 2nd Version [MMSE-2], Rey Auditory Verbal Learning Test [RAVLT], Digit Span, Trail Making Test B [TMT]) to give an indication of the cognitive sequelae on group level.

Reported complaints per daily life activity

We presented the results in percentages of patients or healthy controls reporting complaints per daily life activity (10 activities). The four-point scale was dichotomized into "no complaints" and "complaints". If any complaints were reported ([1] independent with effort, [2] with help, [3] not possible) on at least one of the items within the activity, the participant was classified into the "complaints" category. The percentages of patients and healthy controls who reported that the activity was "not applicable" were reported. In addition, we created a hierarchy among the complaints and differentiated between the level of *restrictions*, *dependence*, and *incapability*. Patients were considered *restricted*, when any restrictions were

reported ([1] independent with effort) on at least one item within the activity. Patients were considered *dependent*, when help was needed ([2] with help) on at least one item within the activity. Patients were considered *uncapable*, when they reported to be uncapable to perform the task ([3] not possible) on at least one of the items within the activity.

Furthermore, the level of fatigue (VAS score) was compared between the patients and the healthy controls per daily life activity using a Mann-Whitney *U* tests (adjusted *p* for 10 tests = .005).

Reported complaints per cognitive domain

We presented the results in percentages of patients or healthy controls reporting complaints per cognitive domain (3 domains). Similar to the procedure mentioned above, we created a hierarchy among the complaints and differentiated between the level of *restrictions*, *dependence*, and *incapability*.

Furthermore, we computed a *total complaint score* (sum score) based on all items as global indication of cognitive complaints. In addition, complaints scores per cognitive domain were computed (i.e., *memory complaint score*, *attention complaint score*, *executive complaint score*). Only items that were applicable for the individual were included (i.e., items rated [0] independent without effort, [1] independent with effort, [2] with help, [3] not possible). To obtain the same range between the scores, the complaints scores were converted to a 0–100 scale with the formula:

$$Complaints\ Score = \frac{\text{Mean score}}{\text{3 (maximum score per item)}} \times 100$$

Higher scores indicated a higher degree of reported complaints. The median and the interquartile range were computed for patients and healthy controls. A Wilcoxon signed-rank test (two related samples) was used to compare the *complaint scores* within the patient group (adjusted *p* for 3 tests = .017).

Comparison between patients' and relatives' reports

A Wilcoxon signed-rank test (two related samples) was used to compare the *complaints scores* (3 domains) between patients and their relatives (adjusted *p* for 3 tests = .017). In addition, a Wilcoxon signed-rank test was used to compare the level of fatigue (mean VAS) per daily life activity (10 activities) as reported by patients and their relatives (adjusted *p* for 10 tests = .005).

Results

Demographic and clinical characteristics

We invited 76 ABI patients to participate and 28 patients declined for several different reasons (e.g., no time, personal reasons). In total, we recruited 48 ABI patients and 107 healthy controls. We had to exclude 2 patients and 4 healthy controls from the current study as no written informed consent was obtained (only verbal consent was given). One healthy control was excluded because she had a neurological disorder (i.e., mild Transient Ischemic Attack [TIA]) in the past. Finally, we included 46 patients and 102 healthy controls for the analyses. From the 46 patients, 33 relatives were included.

See Table 2.3 for demographic and clinical characteristics. Brain lesion was mostly due to a TBI (57%). All patients were in the chronic phase of rehabilitation (> 3 months post ABI onset), and 52% of the patients was either back to work or in process of reintegration. Between the patients and healthy controls, there was no significant difference regarding sex ($\chi^2(1) = .48$, $p = .488$), nor age ($U = 2161.00$, $z = -.77$, $p = .443$), nor education ($\chi^2(2) = 4.81$, $p = .090$). Patients reported a higher level of cognitive complaints (as measured with the *total complaints score*) compared to healthy controls ($U = 216.00$, $z = -8.95$, $p < .001$).

Reported complaints per daily life activity

The highest percentage of patients reported complaints during "contact with friend/family and community" (96%), "leisure activities" (89%), and work/education" (87%) (see Table 2.4). The highest percentage of healthy controls reported complaints during "work/education" (32%), "contact with family/friends and community" (32%), and "cooking" (24%). The percentage of patients reporting *restrictions* (22–46%), *dependence* (0–24%), and *incapability* (2–50%) varied greatly between daily activities (see Table 2.4 and Figure 2.1). The percentage of healthy controls reporting *restrictions* (8–31%), *dependence* (0–6%), and *incapability* (0–3%) varied less. Regarding fatigue, patients reported more fatigue during each daily life activity compared to healthy controls (see Table 2.5).

Reported complaints per cognitive domain

A high percentage of patients reported complaints regarding memory (94%), attention (98%) and executive function (96%), when compared to reported complaints regarding memory (38%), attention (47%), executive function (36%) of healthy controls (see Table 2.6). The highest percentage of patient reported *incapability* (37–65%), when compared to *restrictions* (24–37%) and *dependence* (9–20%). The highest percentage of healthy controls reported *restrictions* (36–44%), when compared to *dependence* (2–6%) and *incapability* (0–3%).

Table 2.3. Demographic and clinical characteristics of the included participants in the quantitative study

	Patients (*n* = 46)		**Relatives** (*n* = 33)	**Healthy controls** (*n* = 102)
Male (%)	52.2		42.4	46.0
Age in years (mean, SD)	46.93 (12.86)		47.84 (11.48)	48.37 (15.09)
Level of education (%)				
Low	4.3		9.1	0
Moderate	28.3		24.2	23.7
High	67.4		66.7	76.3
Type of ABI (%)				
Stroke	32.6			
TBI	56.5			
Brain tumour resection	10.9			
Time ABI onset (median, range)	15 months (3–177)			
Lesion side (%)				
Left	23.9			
Right	30.4			
Bilateral	26.1			
Not visible on scan	17.4			
Unknown	2.2			
Return to work/study (%)				
Completely	8.7			
Yes, but fewer hours	21.7			
In process of reintegration	21.7			
No	34.8			
Unknown	13.1			
MMSE-2 0–30 (mean, SD)	28.9 (1.45)	*n* = 25		
RAVLT percentile				
Immediate (median, < 10th percentile)	18.5 (34.8%)	*n* = 42		
Recall (median, < 10th percentile)	32.5 (23.9%)	*n* = 42		
Recognition 0–30 (median, < 27)	29 (10.9%)	*n* = 42		
Digit Span Scale 0–20				
Total (median, < 7th scale)	10 (21.7%)	*n* = 43		
TMT percentile				
A-B (median, < 10th percentile)	58 (10.8%)	*n* = 43		
Total Complaint Score 0–100 (median, IQR)	30.19 (31.20)		22.81 (31.21)	.95 (3.84)

Abbreviations: Acquired Brain Injury (ABI); Traumatic Brain Injury (TBI); Mini-Mental State Examination – 2nd version (MMSE-2); Rey Auditory Verbal Learning Test (RAVLT); Trail Making Test – version B (TMT-B).

Regarding the *complaints score* of the patients, the median was 26 for *memory*, 42 for *attention*, and 23 for *executive function*. The median for the healthy controls was 0 for each cognitive domain. See Figure 2.2 for the distribution of the *complaints score* per cognitive domain for both groups. The *complaints score* was higher for attention compared to memory (z = -3.96, p <

Table 2.4. Percentage of patients and healthy controls reporting complaints per daily life activity

Patients (*n* = 46)	**N/A (%)**	**No complaints (%)**	**Complaints (%)**	**Restricted (%)**	**Dependent (%)**	**Incapable (%)**
Work/education	8.7	4.3	87	21.8	15.2	50
Leisure activities	0	10.9	89.1	45.6	6.5	37
Travel	6.5	28.3	65.2	36.9	19.6	8.7
Driving	13	32.7	54.3	43.4	0	10.9
Finances	4.3	54.4	41.3	28.3	2.1	10.9
Use of medication	28.3	32.6	39.1	21.7	15.2	2.2
Family life	13	8.7	78.3	28.3	23.9	26.1
Contact family/friends and community	0	4.3	95.7	34.8	10.9	50
Cooking	6.5	8.7	84.8	43.5	8.7	32.6
Grocery shopping	6.7*	22.2	71.1	42.8	17.4	10.9
Healthy controls (*n* = 102)	**N/A (%)**	**No complaints (%)**	**Complaints (%)**	**Restricted (%)**	**Dependent (%)**	**Incapable (%)**
Work/education	2	65.6	32.4	31.4	1	0
Leisure activities	0	85.3	14.7	14.7	0	0
Travel	0	91.2	8.8	7.8	1	0
Driving	7.8	79.5	12.7	12.7	0	0
Finances	0	90.2	9.8	9.8	0	0
Use of medication	50	39.2	10.8	9.8	1	0
Family life	6.9	75.5	17.6	11.7	5.9	0
Contact family/friends and community	0*	68.3	31.7	29.7	0	2
Cooking	4.9	71.6	23.5	18.6	2	2.9
Grocery shopping	1	79.4	19.6	18.6	1	0

Note. We created a hierarchy among the complaints and differentiated between the level of *restrictions*, *dependence*, and *incapability*.
Abbreviations: Not applicable (N/A). * Missing values on all items within the activity for one participant.

.001) and executive functions (z = -5.82, p < .001) within patients. Demographic characteristics (i.e., sex, age and level of education) did not influence the *complaints scores* (memory, attention, executive function) within the current sample of patient with ABI (see Appendix 2.5).

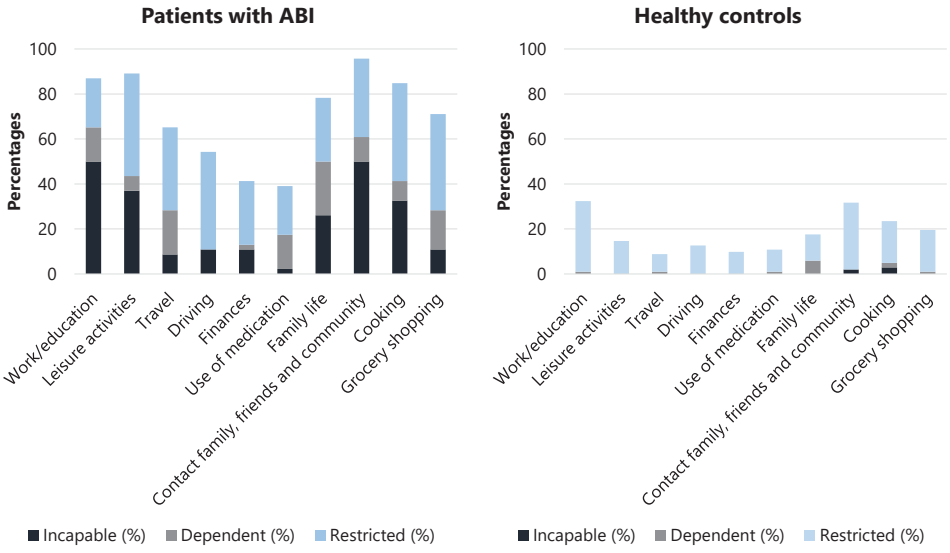

Figure 2.1. Percentage of patients reporting complaints per daily life activity. A hierarchy was created among the complaints and differentiated between the level of restrictions, dependence, and incapability.

Table 2.5. Comparison of the level of fatigue (mean VAS scores) per daily life activity between patients and healthy controls

	VAS score (mean [SD])		**Statistics**
	Patients (n = 46)	**Healthy controls** (n = 102)	**Mann-Whitney *U* tests**
Work/education	7.45 (1.75)	3.16 (2.31)	U = 282.50, z = -7.64, p < .001*
Leisure activities	6.11 (2.47)	1.67 (1.70)	U = 386.00, z = -7.94, p < .001*
Travel	6.08 (2.32)	2.10 (1.95)	U = 474.50, z = -7.35, p < .001*
Driving	5.47 (2.92)	1.90 (1.94)	U = 500.50, z = -5.95, p < .001*
Finances	4.01 (3.19)	1.48 (1.93)	U = 1012.00, z = -4.97, p < .001*
Use of medication	2.03 (2.25)	0.75 (1.19)	U = 532.50, z = -3.34, p = .001*
Family life	6.02 (2.49)	1.34 (1.55)	U = 301.50, z = -7.95, p < .001*
Contact family/friends and community	5.52 (2.59)	1.49 (1.64)	U = 520.50, z = -7.47, p < .001*
Cooking	4.45 (2.92)	1.37 (1.76)	U = 743.00, z = -5.85, p < .001*
Grocery shopping	5.27 (3.17)	1.45 (1.79)	U = 728.50, z = -6.30, p < .001*

* Adjusted p < .005. Note. the number of patients varies as only valid answers (without missing and non-applicable items) are included.

Table 2.6. Percentage of patients and healthy controls reporting complaints per cognitive domain

Patients (*n* = 46)	**N/A (%)**	**No complaints (%)**	**Complaints (%)**	**Restricted (%)**	**Dependent (%)**	**Incapable (%)**	**Range**	**Q1**	**Median**	**Q3**	**IQR**
Memory	0	6.5	93.5	37	19.5	37	0-83	18	26	43	25
Attention	0	2.2	97.8	23.9	8.7	65.2	0-85	26	42	58	32
Executive Function	0	4.3	95.7	24	19.5	52.2	0-57	11	23	43	32
Healthy controls (*n* = 102)	**N/A (%)**	**No complaints (%)**	**Complaints (%)**	**Restricted (%)**	**Dependent (%)**	**Incapable (%)**	**Range**	**Q1**	**Median**	**Q3**	**IQR**
Memory	0	61.8	38.2	36.2	2	0	0-29	0	0	5	5
Attention	0	52.9	47.1	44.2	0	2.9	0-30	0	0	4	4
Executive Function	0	63.7	36.3	28.5	5.8	2	0-27	0	0	3	3

Note. We created a hierarchy among the complaints and differentiated between the level of *restrictions*, *dependence*, and *incapability*. In addition, the median and interquartile range of the complaints score are presented. **Abbreviations:** Not applicable (N/A).

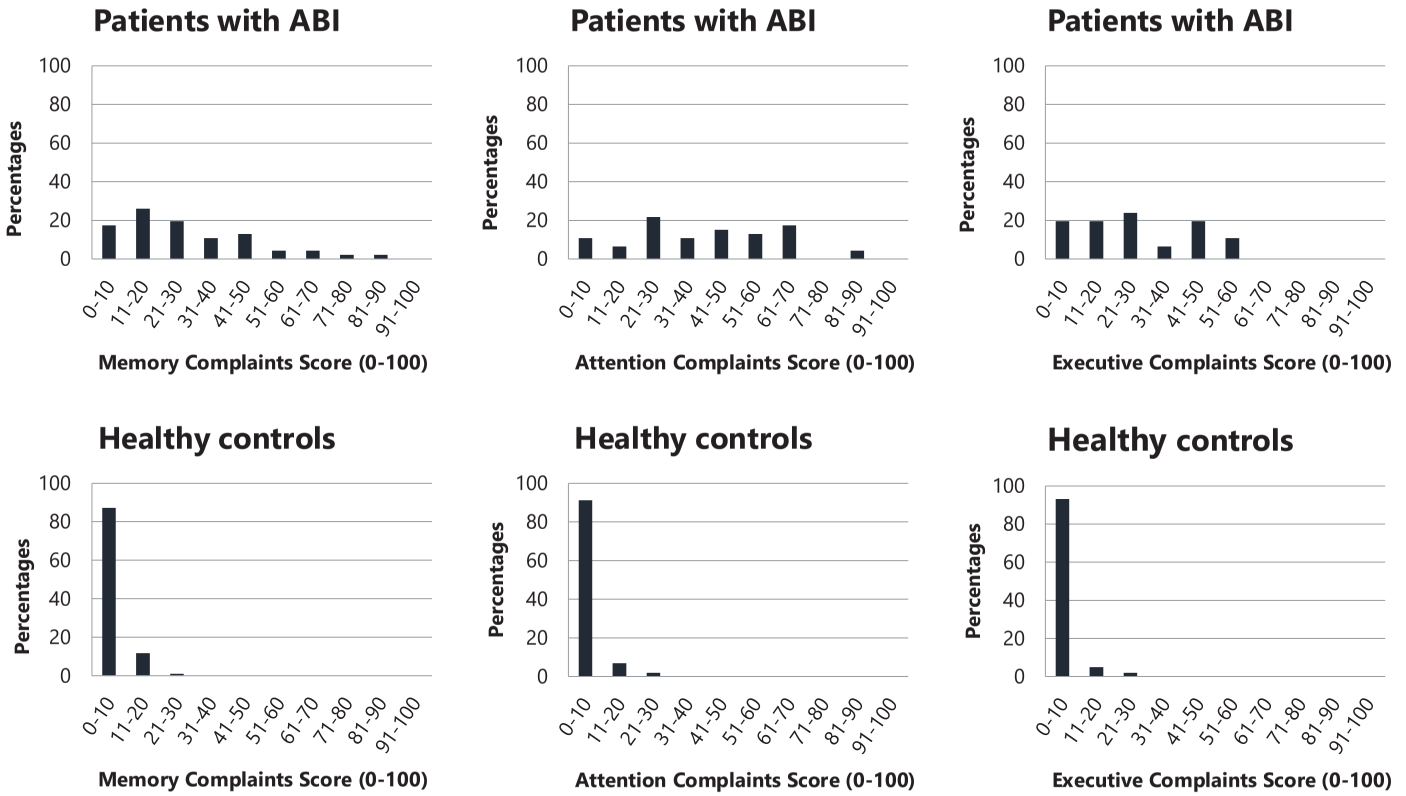

Figure 2.2. The distribution of *complaints scores* for patients with ABI and healthy controls. The converted *complaints scores* to a 0–100 scale are presented on the x-axis. Higher scores indicated a higher degree of reported complaints. The percentages of patients are presented on the y-axis.

Comparison between patients' and relatives' reports

The *complaints scores* of patients were significantly higher for memory and attention, compared to the complaints scores of relatives (see Table 2.7). Patients and relatives had a similar *complaints score* for executive functions. Patients and relatives did not differ on the perceived level of fatigue during the 10 daily life activities (see Table 2.8).

Table 2.7. Comparison of the *complaints scores* (higher scores indicate a higher level of complaints) between patients' and relatives' reports

	Complaints score (median [IQR])		**Statistics**
	Patients (n = 33)	**Relatives** (n = 33)	**Wilcoxon signed-rank test**
Memory complaints score (0–100)	27.78 (25)	19.05 (28)	z = -2.42, p = .015*
Attention complaints score (0–100)	40.00 (34)	26.67 (40)	z = -2.64, p = .008*
Executive complaints score (0–100)	23.33 (33)	19.30 (33)	z = -1.83, p = .067

* Adjusted p < .017.

Table 2.8. Comparison of the level of fatigue (mean VAS score) as reported by patients and their relatives, split per daily life activity

	VAS score (mean [SD])		**Statistics**
Daily life activity	**Patients** (n = 33)	**Relatives** (n = 33)	**Wilcoxon signed-rank test**
Work/education	7.71 (1.58)	7.35 (2.21)	z = -1.06, p = .291
Leisure activities	6.31 (2.24)	5.97 (2.53)	z = -.78, p = .437
Travel	6.22 (1.98)	6.50 (2.32)	z = -.76, p = .446
Driving	5.63 (2.83)	6.22 (3.07)	z = -1.87, p = .062
Finances	4.14 (3.02)	4.01 (2.97)	z = -.86, p = .388
Use of medication	1.88 (2.20)	1.90 (1.94)	z = -.28, p = .778
Family role	5.92 (2.26)	5.87 (2.57)	z = -.34, p = .732
Contact family/friends and community	5.59 (2.33)	5.45 (2.30)	z = -.29, p = .775
Cooking	4.61 (3.02)	4.67 (2.89)	z = -.63, p = .530
Grocery shopping	5.33 (3.04)	5.83 (2.89)	z = -1.50, p = .134

* Adjusted p < .005. Note. the number of patients varies as only valid answers (without missing and non-applicable items) are included.

Discussion

Based on available literature, expert meetings with health professionals and cognitive neuroscientists, semi-structured interviews with patients, and a quantitative study, the inventory *Cognitive Complaints - Participation* (CoCo-P) was developed as a patient- and relative-reported measure to assess cognitive complaints during daily life activities. The majority

of patients (87–96%) who participated in the quantitative study experienced cognitive complaints at work/education, during leisure activities, and/or in contact with family/friends and community. This is probably due to the dynamic and demanding nature of such daily life activities, where one is required to perform multiple operations simultaneously while dealing with environmental distractions (e.g., background noise) and time pressure. Performing adequately in those demanding situations requires more from attentional processes (McCulloch, 2007). Previous literature also reports that the presence of cognitive complaints negatively affects the possibility to return to work (Benedictus et al., 2010; van der Naalt et al., 1999) and the possibility to resume leisure and social activities post ABI (Robison et al., 2009). We found much lower percentages of healthy controls reporting cognitive complaints. However, we found a similar pattern regarding the most affected daily life activities. The highest percentages of heathy controls (31–32%) reported complaints during work/education and in contact with family/friends and community. It is therefore likely that those daily life activities do require more from cognitive processes, compared to other daily life activities. Also, patients reported more fatigue during all daily life activities compared to healthy controls. The fatigue VAS score was considered as an independent measure to give insight in the level of fatigue during daily life activities regardless of the presence or absence of cognitive complaints. Furthermore, we found that complaints related to attention were more frequently reported compared to complaints related to memory or executive functions by patients with ABI. These findings are consistent with a previous review that found a percentage of 29–92% of stroke patients reporting complaints (measured by questionnaires or interviews) about concentration, mental speed and memory (Rijsbergen et al., 2014).

Patients reported more cognitive complaints regarding memory and attention (as measured with the *complaints scores*) than their relatives. This might reflect too little knowledge about the possible consequences of ABI among relatives (Hochstenbach, Prigatano, & Mulder, 2005). Subtle problems and the impact on daily life may not be recognized or understood by relatives, leading to an overestimation of patients' ability (Fordyce & Roueche, 1986; Hochstenbach et al., 2005). For instance, relatives have overestimated patients with ABI in their communication abilities (McClenahan, Johnston, & Densham, 1990, 1992; Seel et al., 1997), or overall functioning (Cavallo, Kay, & Ezrachi, 1992; Cusick, Gerhart, & Mellick, 2000). Previous research shows that agreement tends to be lower for invisible symptoms (e.g., memory problems), but higher for observable symptoms (e.g., writing) (Hochstenbach et al., 2005; Vallat-Azouvi et al., 2018). Fatigue was probably more observable for relatives, hence patients and relatives reported a comparable level of fatigue. A note of caution is due here since we cannot state which underlying process causes the discrepancy between the patients' and relatives' reports. Future research could shed light on this matter.

Strengths and limitations

Involvement of experts, patients and relatives

The strength of this study is the process of development, where we followed a sequence of steps including the consultation of experts and patients. The inventory is based on well-known cognitive models (theory-based) (Petersen & Posner, 1990, 2012; Posner & Rothbart, 2007; Squire, 1992, 2004; Ylvisaker et al., 1998), but also based on the clinical input of healthcare professional and patients (experienced-based). Especially, the patients' engagement in research can potentially lead to an improved development of patient-reported outcomes (Domecq et al., 2014; Wiklund et al., 2016). However, we did not involve the relatives in the development of the relative-reported inventory. Relatives were not interviewed regarding missing daily life activities and specific items. This could be considered as a limitation. However, we do not expect that the involvement of relatives would have resulted in great modifications, because the activities of the CoCo-P can be considered the most characteristic for participation. For instance, previous research suggests that homemaking for others (e.g., cooking), interpersonal relations (e.g., contact with friends and family), major life areas (e.g., work) and community-based roles outside of home or work (e.g., leisure) represent participation (Post et al., 2012; Whiteneck & Dijkers, 2009). These activities are included in the CoCo-P. In addition, the involved patients with mild impairments were considered capable to evaluate the completeness of the daily life activities.

Patient sample

The sample size of the patient group was relatively small. In addition, the group was relatively high-educated and mildly cognitively impaired. Even though the CoCo-P appears to be suitable for all patients with ABI, it remains to be seen how feasible it is for low-educated patients or for patients with moderate to severe cognitive impairments. One might argue that a subjective evaluation of daily life difficulties might be more challenging for patients with a lower education (Boynton, Wood, & Greenhalgh, 2004) or for patients with severe injury-related cognitive impairments (Barrett, 2009; Reeves et al., 2018). Items such as "Do you have attentional problems?" are often considered abstract and challenging by patients. In the CoCo-P, however, the items describe specific cognitive tasks during daily life activities, which is expected to be less challenging. In addition, the frequencies of the cognitive complaints (as measured with the CoCo-P) remain unknown in an ABI population with more severe impairments. Future research should include a larger, more heterogenous sample of patients with respect to type of ABI and severity. This will especially allow the exploration of possible differences in frequencies of complaints between diagnosis-related groups (e.g., stroke, TBI) varying in ABI severity (i.e., mild, moderate, severe).

Given the aim of the current study (developing an inventory to capture cognitive complaints during daily life activities for patient with ABI) the inclusion of patients with mild cognitive impairment could be considered as a strength, as the discrepancy between relatively good test results (on neuropsychological tests) and reported complaints is strikingly common within this group. A novel inventory for systematically assessing cognitive complaints in this group is crucial. This group is also a growing population in rehabilitation medicine, because of the improved neurological treatment (e.g., mechanical thrombectomy, intravenous thrombolytic treatment) and the increased use of early multidisciplinary rehabilitation interventions (Barreto, 2011; Campbell, Donnan, Mitchell, & Davis, 2016; Cifu & Stewart, 1999; Maulden, Gassaway, Horn, Smout, & DeJong, 2005).

Another limitation is the fact that we did not exclude patients with comorbid disorders (e.g., psychiatric or neurological), which might have influenced the frequencies of cognitive complaints. For example, affective disturbances (e.g., depression, irritability, anxiety) can influence subjective reports (Clarke et al., 2012). However, comorbidity is common after ABI (Garrelfs, Donker-Cools, Wind, & Frings-Dresen, 2015), so inviting all patients in the outpatient rehabilitation programme probably increased the representativeness of our sample.

Cognitive domains and subdomains

We selected items focusing on memory (i.e., retrospective memory, prospective memory), attention (i.e., arousal, orienting, monitoring, sustained) or executive function (i.e., planning, self-evaluating, initiative, flexibility) based on well-known cognitive models (Petersen & Posner, 1990, 2012; Posner & Rothbart, 2007; Squire, 1992, 2004; Ylvisaker et al., 1998). The cognitive domains, however, might lack relevant subdomains. For instance, items are missing related to processing speed (as part of attention) and inhibition (as part of executive function), which are commonly impaired in ABI patients (Chung et al., 2013; Cicerone et al., 2000; Veltman, Brouwer, van Zomeren, & van Wolffelaar, 1996). Furthermore, one could argue that the items belong to more than one cognitive (sub)domain, because the cognitive tasks described in the items involve multiple cognitive processes.

Future research

Future research will address the reliability and the validity of the CoCo-P. The reliability could be evaluated in terms of the internal consistency by using the McDonald's omega (McDonald's ω), which is considered the best estimate when the scale in question is multidimensional (Dunn, Baguley, & Brunsden, 2014; Watkins, 2017; Zinbarg, Revelle, Yovel, & Li, 2005). The calculation of the McDonald's ω requires the application of a factor analytic model, which requires a large sample size (Watkins, 2017; Zinbarg, Yovel, Revelle, & McDonald, 2006).

A factor analytic model will identify the structure of the inventory by revealing whether the items reflect the three underlying and independent cognitive domains (i.e., memory, attention, executive function). Next, the validity should be addressed in terms of construct validity (i.e., examination whether the inventory measures the theoretical constructs of interest) by estimating its association with other patient-reported measures (e.g., USER-P, CLCE-24). Furthermore, the *complaints scores* per cognitive domain could be compared with the scores on a neuropsychological assessment, which would reveal the relation between the reported complaints and underlying cognitive impairments. Finally, we found that healthy controls are unlikely to show a *complaint score* higher than 5 per cognitive domain (highest Q3 = 5 for the *memory complaint score*). The *complaints scores* are easy to use clinically and seems appropriate in differentiating between cognitively healthy controls and patients reporting cognitive complaints. However, more established analyses are needed to determine a valid cut-off score. Future research should focus on investigating the sensitivity and specificity (positive and negative predicted value) in relation to an external instrument measuring cognitive complaints (e.g., CLCE-24).

Clinical implications

Especially during outpatients rehabilitation, the primary goals are to maximize functional independence and participation (Post et al., 2012; Wade & de Jong, 2000). Neuropsychological assessment examines the cognitive impairments that could hamper participation. Cognitive complaints may also negatively affect participation. For this reason, previous research emphasized the need for patient-reported measures to capture and quantify the difficulties patients encounter in daily life (Carrigan & Barkus, 2016; Meadows, 2011; Wiklund et al., 2016). The CoCo-P can complement a neuropsychological assessment by capturing the subjective cognitive complaints in a standardized manner, and, just as important, by assessing the impact of cognitive complaints on participation. The CoCo-P can be used in a multidisciplinary team (e.g., neuropsychologists, occupational therapists) to determine the focus of the intervention (activity-focused/domain-focused). Finally, the CoCo-P can be used as a metric to assess cognitive complaints longitudinally and to evaluate the effect of the intervention.

Conclusions

In conclusion, the CoCo-P is a patient- and relative-reported measure to assess cognitive complaints during daily life activities in patients with ABI. The majority of patients (87–96%) experienced cognitive complaints at work/education, during leisure activities, and in contact with family/friends and community. The CoCo-P can be used to capture the subjective

cognitive complaints in a standardized manner, and, just as important, to assess the impact of the cognitive complaints on participation. The *complaints scores* per cognitive domain are easy to use clinically and seems appropriate to differentiate between cognitively healthy controls and patients reporting cognitive complaints in daily life. Future research will address the reliability and validity of the CoCo-P.

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Appendix 2.1. An overview of instruments measuring cognitive complaints or participation

Cognitive Complaints

Stroke Impact Scale (SIS) *subscale memory and thinking*
Cognitive Failure Questionnaire (CFQ)
Checklist for Emotional and Cognitive Consequences (CLCE-24)
Utrecht Scale for Evaluation of Clinical Rehabilitation (USER) *subscale cognitive functioning*
Brain Injury Complaint Questionnaire (BICoQ)
Cerebral Visual Disorders (CVD)
Screening Test for Cognitive Communication (STCC)
Communicative Participation Item Bank (CPIB)

Level of Participation and/or activity

Utrecht Scale for Evaluation of Clinical Rehabilitation – Participation (USER-P)
Stroke Impact Scale (SIS) *subscale ability to participate*
Instrumental Activities of Daily Living (IADL)
Frenchay Activities Index (FAI)
Assessment of Life-Habits (Life-H)
Participation Measure - Post Acute Care (PM-PAC)
ICF Measure of Participation and Activities questionnaire (IMPACT-S)
Outcome Questionnaire (OQ-45) *subscale social role performance*

Appendix 2.2. An overview of the percentages of healthy controls (n = 102) reporting complaints per item on the preliminary inventory used in the quantitative study

			No complaints (%)	Complaints (%)	Not applicable (%)	Missing (%)
Memory	*Retrospective*	6) Remembering information	82	12	6	0
		11) Remembering related people	99	1	0	0
		17) Remembering unfamiliar routes	65	26*	9	0
		26) Remembering events or conversations	82	11	7	0
		30) Remembering names of family members/friends	95	4	0	1
		32) Remembering names of people I just met	52	48*	0	0
		36) Remembering the order	84	9	6	1
	Prospective	14) Remembering the arrival/departure time	77	23*	0	0
		22) Remembering taking my medication	44	7	49	0
		41) Remembering the products	80	19	1	0
Attention	*Arousal*	8) Staying awake during activities	96	4	0	0
		16) Staying awake while driving	88	4	8	0
	Orienting	15) Paying attention to other road users	92	0	8	0
		28) Conversing in busy surroundings	83	16	0	1
	Monitoring	3) Performing my activities in busy surroundings	80	13	7	0
		4) Tolerating bright displays	92	5	3	0
	Sustained	2) Paying attention to my work	79	19	2	0
		5) Performing activities without extra breaks	85	10	5	0
		9) Doing several activities consecutively	91	9	0	0
		29) Maintaining social events without extra breaks	89	10	0	1
		35) Paying attention to cooking	86	8	6	0

Appendix 2.2. *Continued*

			No complaints (%)	Complaints (%)	Not applicable (%)	Missing (%)
Executive Functions	*Planning*	1) Planning activities for the day/week	95	2	3	0
		12) Planning a journey	93	7	0	0
		19) Planning my budget and spending	87	10	3	0
		21) Planning prescription refill	44	5	51	0
		24) Intake of medication at fixed times	42	7	51	0
		34) Checking ingredients before cooking	91	3	6	0
		38) Accurately estimating the time	83	10	7	0
		40) Planning the needed products	91	6	3	0
		42) Finding the products	92	7	1	0
	Self-evaluating	7) Checking my work	90	6	3	1
		18) Maintaining the appropriate speed	83	9	8	0
		37) Maintaining the right temperature	91	4	5	0
	Initiative	10) Performing leisure activities	97	3	0	0
		20) Paying the bills on time	96	2	2	0
		23) Taking my medication	47	1	52	0
		25) Organizing activities for my family	84	9	7	0
		27) Participating in family life	91	1	8	0
		31) Maintaining contact with family/friends	87	12	0	1
		33) Making appointments	95	4	1	0
	Flexibility	13) Adjusting the plan	96	4	0	0
		39) Multitasking while cooking	86	10	4	0

* More than 20% of healthy controls reporting complaints.

Appendix 2.3. An overview of the percentages of patients with ABI ($n = 46$) reporting complaints per item on the preliminary inventory used in the quantitative study

			No complaints (%)	Complaints (%)	Not applicable (%)	Missing (%)
Memory	*Retrospective*	6) Remembering information	15	72	13	0
		11) Remembering related people	59	37	2	2
		17) Remembering unfamiliar routes	26	59	15	0
		26) Remembering events or conversations	24	67	9	0
		30) Remembering names of family members/friends	72	28	0	0
		32) Remembering names of people I just met	15	85	0	0
		36) Remembering the order	46	46	7	2
	Prospective	14) Remembering the arrival/departure time	22	67	11	0
		22) Remembering taking my medication	39	33	28**	0
		41) Remembering the products	20	72	7	2
Attention	*Arousal*	8) Staying awake during activities	59	39	0	2
		16) Staying awake while driving	54	30	15	0
	Orienting	15) Paying attention to other road users	41	46	13	0
		28) Conversing in busy surroundings	9	91	0	0
	Monitoring	3) Performing my activities in busy surroundings	7	80	13	0
		4) Tolerating bright displays	43	48	7	2
	Sustained	2) Paying attention to my work	17	72	8	2
		5) Performing activities without extra breaks	4	76	20	0
		9) Doing several activities consecutively	13	87	0	0
		29) Maintaining social events without extra breaks	11	87	2	0
		35) Paying attention to cooking	28	63	7	2

Appendix 2.3. *Continued*

			No complaints (%)	Complaints (%)	Not applicable (%)	Missing (%)
Executive Functions	*Planning*	1) Planning activities for the day/week	37	52	11	0
		12) Planning a journey	33	59	9	0
		19) Planning my budget and spending	54	39	7	0
		21) Planning prescription refill	43	24	33**	0
		24) Intake of medication at fixed times	48	20	33**	0
		34) Checking ingredients before cooking	52	37	0	11
		38) Accurately estimating the time	41	48	11	0
		40) Planning the needed products	35	54	9	2
		42) Finding the products	41	48	4	7
	Self-evaluating	7) Checking my work	28	57	15	0
		18) Maintaining the appropriate speed	54	30	15	0
		37) Maintaining the right temperature	72	22	7	0
	Initiative	10) Performing leisure activities	33	61	4	2
		20) Paying the bills on time	67	22	11	0
		23) Taking my medication	67	4*	28**	0
		25) Organizing activities for my family	17	63	20	0
		27) Participating in family life	15	70	15	0
		31) Maintaining contact with family/friends	33	67	0	0
		33) Making appointments	61	39	0	0
	Flexibility	13) Adjusting the plan	35	50	15	0
		39) Multitasking while cooking	13	80	7	0

* Less than 10% of patients reporting complaints; ** More than 25% of patients reporting the task is not applicable.

Work and/or education

THIS INCLUDES PAID WORK, VOLUNTARY WORK, AND PART-TIME OR FULL-TIME EDUCATION.

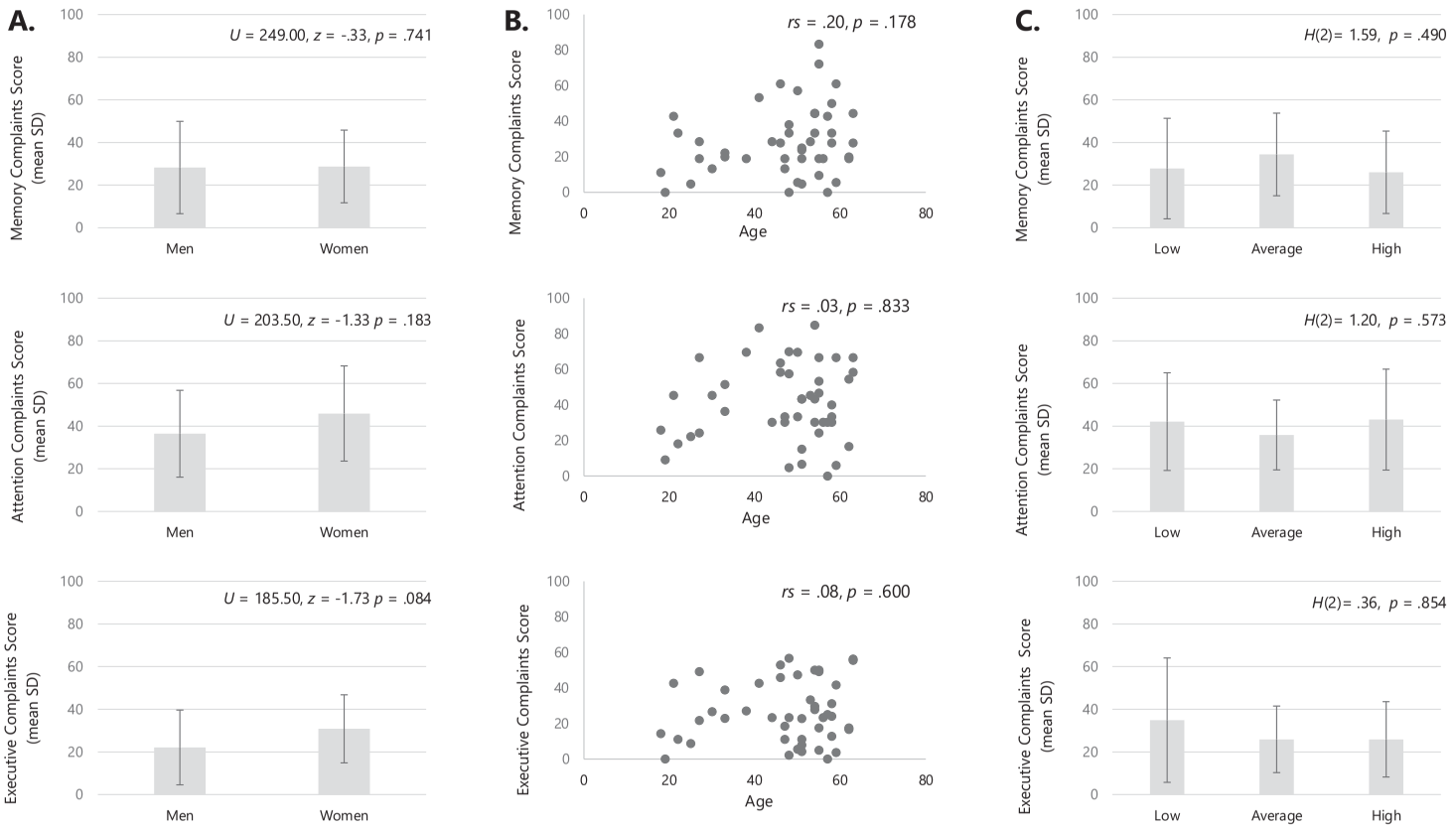
Please answer each question in relation to the brain injury.	Independently without effort	Independently with effort	With help	Not possible	Not applicable
1. I plan my activities for the day and the week.	○	○	○	○	○
2. I pay attention to my work, without being distracted by things that happen around me.	○	○	○	○	○
3. I can carry out my tasks and activities in busy surroundings.	○	○	○	○	○
4. I can tolerate looking at a bright computer screen, tablet computer or phone.	○	○	○	○	○
5. I have enough mental energy for tasks at my work/education. I do not need to take extra breaks.	○	○	○	○	○
6. I remember the information I heard at work meetings or during classes.	○	○	○	○	○
7. I check my completed tasks and activities and decide what still needs to be done.	○	○	○	○	○

ADDITIONAL REMARKS:

How tiring is your work/education for you?

not tiring at all _____ **extremely tiring**

Appendix 2.4. Preview of the CoCo-P patient version translated in English. Note that this study was conducted with the use of the Dutch version of the inventory (the Dutch version is available on https://www.kcrutrecht.nl/project/coco-p/).



Appendix 2.5. **(a)** Average *memory complaints score*, *attention complaints score*, *executive complaints score* for patients with ABI split for sex; **(b)** Relation between *memory complaints score*, *attention complaints score*, *executive complaints score* and age for patients with ABI; **(c)** Average *memory complaints score*, *attention complaints score*, *executive complaints score* for patients with ABI split for level of education.

Part II

Digital neuropsychological tests

On August 22nd in 2016, I drove my bicycle to work and crossed the street while the traffic light was orange. I was hit by a car and I ended up on the windshield, hitting my head on the boarder. A doctor was transported by a helicopter to the scene of the accident. The doctor intubated me and brought me to sleep. I was transported to the hospital by ambulance. I was in a coma for 10 days. They removed a part of my skull to release the pressure on my brain. I was admitted for 10 more days on the neurosurgery ward, but I was still not really present. When I awoke, I could not sit, speak, nor eat and I had difficulty breathing. When I started to realize what happened to me, I was angry. I used to be an athlete and studied at the university. Those things were no longer possible. In one weekend, I recovered quite quickly and I was admitted to a rehabilitation center for eight months. I could barely talk, as I mixed up three languages interchangeably. I had trouble remembering new information and I felt like others were talking too fast. I often wondered, what it is that I am actually suffering from? Neuropsychological assessment was useful as it gave me insight into my shortcomings. I think it had been easier if I was not able to walk anymore for the rest of my life, instead of suffering from a brain injury. Brain injuries are often poorly understood and the long-term consequences are sometimes unclear. The car accident changed my way of thinking. Before the accident I aimed for the highest possible. Now, I am just happy to be alive and I enjoy every day.

Chapter 3

Digital neuropsychological assessment: Feasibility and applicability in patients with acquired brain injury

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Abstract

Introduction: Digital neuropsychological assessment (d-NPA) has several advantages over paper-and-pencil tests in neuropsychological assessment, such as a more standardized stimulus presentation and response acquisition. We investigated (1) the feasibility and user-experience of a d-NPA in patients with acquired brain injury (ABI) and healthy controls; (2) the applicability of conventional paper-and-pencil norms on digital tests; and (3) whether familiarity with a tablet would affect test performance on a tablet.

Method: We administered a d-NPA in stroke patients (n = 59), traumatic brain injury patients (n = 61) and healthy controls (n = 159). The neuropsychological tests were presented on a tablet and participants used a pencil stylus to respond. We examined the completion rate to assess the feasibility, and a semi-structured interview was conducted to examine the user-experience. The applicability of conventional norms was examined by the number of healthy controls performing < 10^{th} percentile, which was expected to be no more than 10%. The effect of tablet familiarity on test performance was examined with a regression-based model.

Results: Overall, 94% of patients completed the d-NPA. The d-NPA was considered pleasant by patients and healthy controls. Conventional norms that exist for paper-and-pencil tests were not applicable on the digital version of the tests, as up to 34% of healthy controls showed an abnormal performance on half of the tests. Tablet familiarity did not affect test performance on a tablet, indicating that participants who were more experienced with working with a tablet did not perform better on digital tests.

Conclusions: The administration of a d-NPA is feasible in patients with ABI. Familiarity with a tablet did not impact test performance, which is particularly important in neuropsychological assessment. Future research should focus on developing norms in order to implement a d-NPA in clinical practice.

Introduction

Neuropsychological paper-and-pencil tests are widely used to assess cognitive functioning. Their validity and reliability have been evaluated and documented thoroughly (International Test Commission, 2001; Lezak, Howieson, Loring, Hannay, & Fischer, 2004; Muñiz & Bartram, 2007). Over the last decades, computerized tests and test batteries have been developed to administer, score, and interpret measures of cognitive functioning (Kane & Kay, 1992; Parsey & Schmitter-Edgecombe, 2013; Rabin et al., 2014). Computerized tests have several advantages over paper-and-pencil tests, as they allow a more standardized stimulus presentation and response acquisition, automated scoring (which is cost and time efficient and less prone to errors), and a convenient data storage (Bauer et al., 2012; Cernich, Brennana, Barker, & Bleiberg, 2007). Some computerized test batteries translated conventional paper-and-pencil tests into computerized tests, and other test batteries developed new tests (see Appendix 3.1 for an overview of computerized test batteries).

There are, however, several aspects that compromise the usability of computerized test batteries in clinical practice (Bauer et al., 2012; Bilder & Reise, 2019; Schlegel & Gilliland, 2007). For instance, introducing new tests in clinical practice requires clinicians to invest time in learning the structures, instructions and underlying constructs of the tests. In addition, norm scores of computerized test batteries are often not available (Canini et al., 2014; Schlegel & Gilliland, 2007). Furthermore, some test batteries allow self-administration with minimal interaction between the clinician and patient. Important behavioural observations, such as fatigue or unexpected distractors, are therefore lost (Bilder & Reise, 2019; Harvey, 2012; Kaplan, 1988; Witt, Alpherts, & Helmstaedter, 2013). Finally, an individual's familiarity with a response device (e.g., keyboard, computer mouse, joystick or touch-screen devices) may affect test performance (Germine, Reinecke, & Chaytor, 2019). For instance, people with greater computer experience tend to perform better on computerized tests than those with less computer experience (Iverson, Brooks, Ashton, Johnson, & Gualtieri, 2009; Tun & Lachman, 2010). Previous studies – where several response devices were compared – concluded that touch-screen devices are considered favourable in cognitive assessment, due to an intuitive and natural interaction (Canini et al., 2014; Carr, Woods, & Moore, 1986; Findlater, Froehlich, Fattal, Wobbrock, & Dastyar, 2013; Murata & Iwase, 2005). Since touch-screen devices require little training, little cognitive demands, and little hand-eye coordination, they have been considered especially suitable among people who are less exposed to technology (Canini et al., 2014; Cernich et al., 2007; Joddrell & Astell, 2016). However, further research is needed regarding the potential effect of familiarity with touchscreen devices on test performance (Germine et al., 2019; Jenkins, Lindsay, Eslambolchilar, Thornton, & Tales, 2016; Joddrell & Astell, 2016; Wallace et al., 2019).

In this study, we investigated a digital neuropsychological assessment (d-NPA) containing twelve conventional paper-and-pencil tests that were translated to digital tests. The d-NPA was administered by a neuropsychologist so no behavioural observations would be lost. The digital tests were presented on a touch-screen device (i.e., tablet) and participants used a pencil stylus to respond. Our first aim was to investigate the feasibility and user-experience in patients with acquired brain injury (ABI) and healthy controls. This is important as patients with ABI may experience sensory overload when using technological devices, in particular in demanding or stressful situations (Scheydt et al., 2017). In order to gain diagnosis-specific insights, we recruited patients with stroke and patients with traumatic brain injury (TBI), which are the most common causes of ABI. Second, as a paper-and-pencil administration differs from a digital administration, norms that exists for paper-and-pencil tests may not simply be applicable to digital versions of the tests, even though the structure, instructions and underlying constructs remain similar (Bauer et al., 2012; Germine et al., 2019; Parsey & Schmitter-Edgecombe, 2013). Therefore, we investigated the applicability of conventional norms that exist for paper-and-pencil tests on our digital versions of the tests. Conventional norms correct for an effect of age, sex and/or level of education (Heaton, I., & Matthews, 1986). However, technology-specific factors might impact test performance as well (American Psychological Association, 1986). Since familiarity with a particular response device seems to be an important factor (Germine et al., 2019; Jenkins et al., 2016), our third aim was to investigate whether familiarity with a tablet influenced test performance on a d-NPA and should be taken into account in future norms.

Methods

Participants

We recruited participants between April 2017 and April 2018. Stroke and TBI patients who were treated at the *University Medical Centre Utrecht* or *De Hoogstraat Rehabilitation Centre*, the Netherlands, between January 2015 and April 2018, were considered for inclusion. The inclusion criteria were: (1) clinically diagnosed stroke as indicated by clinical computed tomography (CT) or magnetic resonance imaging (MRI) scan, and clinically diagnosed TBI as indicated by a neurologist; (2) aged ≥ 18 years; (3) fluent in Dutch; and (4) living at home at the time of participation. We excluded patients with severe communication and/or language deficits (evaluated by researcher) to prevent unreliable test performances, as language deficits would hamper the understanding of test instructions and providing verbal responses. Eligible patients were invited to participate via an information brochure that was handed out by a clinician (e.g., rehabilitation specialist, occupational therapist) or send by

post. The research session took place at the medical centre, the rehabilitation centre, or at a patient's home.

As a reference group, healthy controls were recruited among acquaintances of the researchers, via (sport) clubs, and via social media. The data of an additional group of healthy controls was obtained from Philips Research who conducted a similar study to enlarge the sample and its generalizability. These participants were recruited from a proprietary database of elderly people. Overall, the inclusion criteria of the healthy controls were: (1) aged ≥ 18 years; and (2) fluent in Dutch. We excluded participants with a medical history of neurological and/or psychiatric disorders for which medical treatment was necessary (based on self-report). All participants gave written informed consent. The research protocol of the current study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht (METC protocol number 16-760/C). The study was performed in accordance with the Declaration of Helsinki.

Digital Neuropsychological Assessment (d-NPA)

A trained neuropsychologist (one licenced and four residents) administered the twelve tests of the d-NPA in a fixed order: Rey Auditory Verbal Learning Test (RAVLT) immediate recall, Trail Making Test (TMT) part A and B, Cube Drawing, O-Cancellation, Clock Drawing, Star Cancellation, RAVLT delayed recall and recognition, Rey-Osterrieth Complex Figure (ROCF) copy, Verbal Fluency Letter, ROCF immediate recall, Digit Span forwards and backwards, Verbal Fluency Category, Stroop Colour and Word Test (Stroop), ROCF delayed recall, and the Wisconsin Card Sorting Test (WCST). See Appendix 3.2 for references to the used stimuli, instructions and scoring, the outcome measures, and the conventional norms.

The software of the d-NPA was a research prototype developed by Philips Research (Vermeent et al., 2020). The software included test descriptions, test instructions, administration forms to record observations, and stimuli (auditory and visual). It was designed to be used on a regular laptop (HP© EliteBook840) in combination with a tablet (Apple© iPad Pro) with a screen size of 12.9-inch and a screen resolution of 2732 × 2048 pixels. Participants used a pencil stylus (Apple© Pencil) on the tablet to conduct drawing tests or tests that needed a manual response. A tablet was placed in front of the participant and the neuropsychologist sat across them while controlling the tests on a regular laptop. The brightness of the tablet screen and the volume of the laptop were set to 100%.

Verbal responses (RAVLT, Verbal Fluency, Digital Span, Stroop) were recorded by the audio recorder on the tablet and scored on the laptop during and/or after the administration by the neuropsychologist. Manual responses (O-cancellation, Star Cancellation, TMT,

WCST) were recorded and scored automatically, but corrected based on observations of the neuropsychologist if necessary (e.g., if a non-target was unintentionally marked by the touch of the hand on the screen). Manual responses of drawing tests (Cube drawing, Clock drawing, ROCF) were recorded automatically and could be replayed. The scoring of drawing tests was done afterwards by the neuropsychologist.

Semi-structured interview on user-experience

At the end of the test assessment, the neuropsychologist conducted a semi-structured interview consisting of eight questions: (1) What do you think about performing the tests on a tablet?; (2) How was the visibility of the tests?; (3) How difficult was drawing on a tablet screen?; (4a) How comparable was drawing on a tablet screen with drawing on paper?; (4b) What were the differences between drawing on a tablet screen and drawing on paper?; (5) Could you draw as precisely on a tablet screen as on paper?; (6) How accurate was the appearance of your drawing on the tablet screen?; (7) Was there a touch latency between the moment you drew and the appearance of your drawing on the tablet screen?; and (8) What improvements can be made? Response options ranged from 1 (negative) to 5 (positive) with different labels for each question, except for question 7, which could be answered with "yes" or "no". Question 4b and 8 were open-ended questions.

Demographic and clinical characteristics

We collected data on sex, age and level of education. Level of education was scored according to a Dutch classification system (Verhage, 1965), consisting of 7 levels, with 1 being the lowest (less than primary school) and 7 being the highest (academic degree). These levels were converted into three categories for analysis: low (Verhage 1–4), average (Verhage 5), and high (Verhage 6–7). This classification system is the most commonly used system in the Netherlands and is similar to the International Standard Classification of Education (UNESCO, 1997). We asked participants whether they used a tablet regularly, and, if yes, how many hours per week they used it. At the beginning of the test session, the conventional Mini-Mental State Examination – 2nd Edition (MMSE-2) was administered as measure of general cognitive functioning (Folstein, Folstein, White, & Messer, 2010). For stroke patients, we extracted time since stroke, stroke type (ischaemic, haemorrhage or subarachnoid haemorrhage) and lesion side (left, right or both) from the medical files. For TBI patients, we extracted the time since injury, CT abnormalities (yes/no), and cause of injury (collision, fall, or other) from the medical files.

Statistical analysis

Demographic and clinical characteristics

Non-parametric tests (Kruskal-Wallis non-parametric ANOVA and post-hoc Mann-Whitney *U* test for continuous variables, and Chi-square test for categorical variables) were used to compare the demographic characteristics, tablet use, and global cognitive functioning between groups.

Feasibility and user-experience

To evaluate feasibility, we reported the number of stroke and TBI patients: (1) who did not complete one or more tests; (2) who needed more than one break during the test session; (3) for whom the brightness of the tablet screen had to be brought down to 50%; and (4) for whom the volume of the laptop needed to be turned down. To evaluate user-experience, we reported the responses for each closed-ended question of the semi-structured interview, split for stroke patients, TBI patients and healthy controls. For the open-ended questions, we described the answers that were provided by ≥ 5% of the participants.

Applicability of conventional norms on digital tests

Dutch conventional norms were applied to the raw scores of each outcome measure (See Appendix 3.2)[1]. The percentages of healthy controls, stroke patients and TBI patients who performed below the 10th percentile or below cut-off (RAVLT recognition, Cube Drawing, Clock Drawing, O-cancellation, Star Cancellation) were reported. Based on Lezak's distribution, we expected that < 10% of the healthy controls would perform below the 10th percentile (Lezak, Howieson, Bigler, & Tranel, 2012). Regarding the stroke and TBI patients, we expected that > 10% would perform below the 10th percentile, because of the expected cognitive disorders in these populations.

Effect of tablet familiarity on test performance

Based on the data of healthy controls, multiple linear regression analyses were conducted to explore the effect of tablet familiarity on test performance on each test of the d-NPA. The raw scores of the tests were used as outcome variables. We chose a hierarchical method (blockwise entry) where predictors were grouped into blocks. Age (in years), sex (coded as 0 [men] and 1 [women]) and level of education (dummy coded with average education

[1] The Stroop was not included in these analyses. Dutch clinical norms of the Stroop are based on stimuli where subsequent colors are sometimes the same (e.g., red, red, red), whereas our digital version included stimuli where subsequent colors are never the same (Hammes, 1973). The clinical norms were therefore not applicable to our digital version of the test, as pronouncing the same color subsequently improves velocity.

as reference category) were used as predictors in the first block of the hierarchy (model 1). Tablet familiarity (use of tablet in hours per week) was added to the second block of the hierarchy (model 2). We evaluated the improvement of model 2 compared to model 1 by looking at the *F*-change and whether this change was significant. A Benjamini-Hochberg correction was applied to counteract the problem of multiple comparisons (Benjamini & Hochberg, 1995), which is considered the best approach in exploratory research (false discovery rate was set at .1).

Several assumptions were evaluated as followed: (1) multicollinearity between predictors was examined by inspecting Pearson's correlation coefficient (no significant correlations > .7); (2) independence of observations was evaluated by Durbin–Watson tests (values below 1 and above 3 are cause for concern); (3) the linearity and homoscedasticity were examined using scatter plots of residuals; (4) normality of residuals was examined by using probability-probability (p-p) plots; and (5) influential cases were identified by computing Cook's distances.

Results

Demographic and clinical characteristics

We invited 498 patients, of whom 378 patients did not respond or declined due to several reasons (e.g., no time/interest, personal reasons). We included 59 stroke patients and 61 TBI patients in our study. In addition, we included 56 healthy controls. We obtained d-NPA data of 103 healthy controls (from Philips Research), resulting in a total of 159 healthy controls. See Table 3.1 for the demographic and clinical characteristics.

The healthy control group and patient groups were comparable regarding the distribution of sex, education, handedness, global cognitive functioning and tablet use (% yes). There were no significant differences in the average number of hours they used a tablet per week (Table 3.1). Healthy controls were significantly older compared to stroke patients ($U = 3587.50$, $z = -2.67$, $p = .008$) and TBI patients ($U = 2688.00$, $z = -5.12$, $p < .001$).

Feasibility

The majority of the patients (94%) was able to complete the entire d-NPA (Table 3.2). One stroke patient was not able to complete the ROCF and not able to start the Stroop and the WCST, as the patient reported to be too tired. One TBI patient did not complete four tests (i.e., TMT, O-Cancellation, Star Cancellation, Stroop) due to sensory overload caused by the high density of stimuli (as reported by the patient). Of the five TBI patients who did not

Table 3.1. Demographic and clinical characteristics

	Patients with stroke (*n* = 59)	**Patients with TBI** (*n* = 61)	**Healthy controls** (*n* = 159)	**Statistics**
Male (%)	64.4	50.8	59.1	$\chi^2(2) = 2.35$, $p = .308$
Age in years (mean, SD)	54.02 (13.26)	46.48 (16.21)	58.38 (13.82)	$H(2) = 28.31$, $p < .001$
Range	22-79	18-73	21-81	
Level of education (%)				$\chi^2(4) = 2.98$, $p = .561$
Low	13.6	9.8	8.2	
Average	27.1	21.3	20.8	
High	59.3	68.9	71.1	
Handedness* (%)				$\chi^2(4) = 5.31$, $p = .257$
Left	15.3	13.1	6.3	
Right	83.1	83.6	91.2	
Ambidextrous	1.7	3.3	2.5	
Tablet use (% yes)	67.8	65.6	65.4	$\chi^2(2) = .11$, $p = .945$
Tablet use hours per week (mean, SD)	5.29 (7.91)	6.29 (8.79)	5.49 (8.31)	$H(2) = .075$, $p = .963$
MMSE-2 (0–30) (mean, SD)	28.32 (1.96)	28.82 (1.37)	28.67 (1.43)	$H(2) = 1.66$, $p = .437$
Below cut-off of 24 (%)	1	1	1	
Time since stroke/TBI (mean)	19.4 months	45.8 months		
Range	(4–268)	(5–386)		
Stroke type (%)				
Ischaemic	47.5			
Haemorrhage	8.5			
Subarachnoid haemorrhage	44.1			
Lesion side (%)				
Left	33.9			
Right	33.9			
Bilateral	15.3			
Not visible on scan	16.9			
CT abnormalities (%)				
Yes		54.1		
No		21.3		
Unknown		24.6		
Cause of injury (%)				
Collision		49.2		
Fall		41.0		
Other		9.8		
Testing site (%)				
University Medical Centre	73	48	19	
Rehabilitation Centre	7	31	4	
Participant's home	20	21	12	
Data obtained from Philips			65	

Abbreviations: Acquired Brain Injury (ABI), Computer Tomography (CT), Mini-Mental State Examination – 2nd version (MMSE-2), Standard Deviation (SD), Traumatic Brain Injury (TBI). *All patients used their dominant hand to perform the tests on the tablet, yet two patients whose injury affected the dominant hand used their non-dominant or both hands alternating.

complete 1 to 2 tests, three patients additionally needed a reduction of the brightness, an adjustment of the volume, and/or an extra break. Of all patients, 5% needed an extra break and 6% needed technological adjustments.

Table 3.2. Feasibility of a digital administration of a neuropsychological assessment in stroke and TBI patients

	Patients with stroke (*n* = 59)	**Patients with TBI** (*n* = 61)
Completion d-NPA (%)	98.3 (*n* = 58)	90.2 (*n* = 55)
1–2 tests not completed (%)	0	8.2 (*n* = 5)
> 2 tests not completed (%)	1.7 (*n* = 1)	1.6 (*n* = 1)
Need for extra break (%)	0	9.8 (*n* = 6)
Reduced brightness (%)	0	8.2 (*n* = 5)
Lowered sound volume (%)	1.7 (*n* = 1)	1.6 (*n* = 1)

Abbreviations: digital neuropsychological assessment (d-NPA), Traumatic Brain Injury (TBI).
Note. These observational measures were systematically administered in 56 healthy controls only. All of the healthy controls completed the d-NPA, and none of them needed an extra break, an adjustment of the brightness or sound volume.

User-experience

The majority of the participants (91%) considered performing the tests on a tablet as pleasant or very pleasant (Figure 3.1; question 1). Four patients reported the experience as (very) unpleasant, of which one TBI patient aborted four tests and one TBI patient aborted one test and needed an extra break and a reduction of the brightness. These patients reported that the unpleasant experience was caused by the brightness of the tablet screen which resulted in sensory overload (e.g., they felt it was tiring, required more mental energy). The visibility of the tests (question 2), the difficulty of drawing (question 3), and the appearance of the drawing (question 6) were considered satisfactory for patients and healthy controls. The majority of the participants (91%) reported there was no touch latency between the moment the participant drew and the appearance of the drawing on the tablet screen.

Different responses were provided regarding the precision of drawing on a tablet screen, with patients being more positive than healthy controls (question 5). Most patients and healthy controls reported that drawing on a tablet screen was quite similar with drawing on paper (question 4), however, there were noteworthy differences: the surface of the tablet screen gave less friction compared to drawing on paper (47%); drawing on a tablet screen was less accurate compared to drawing on paper (18%); errors could not be erased on the tablet (12%); one was not able to rest his/her hand on the tablet (9%); different manual feedback

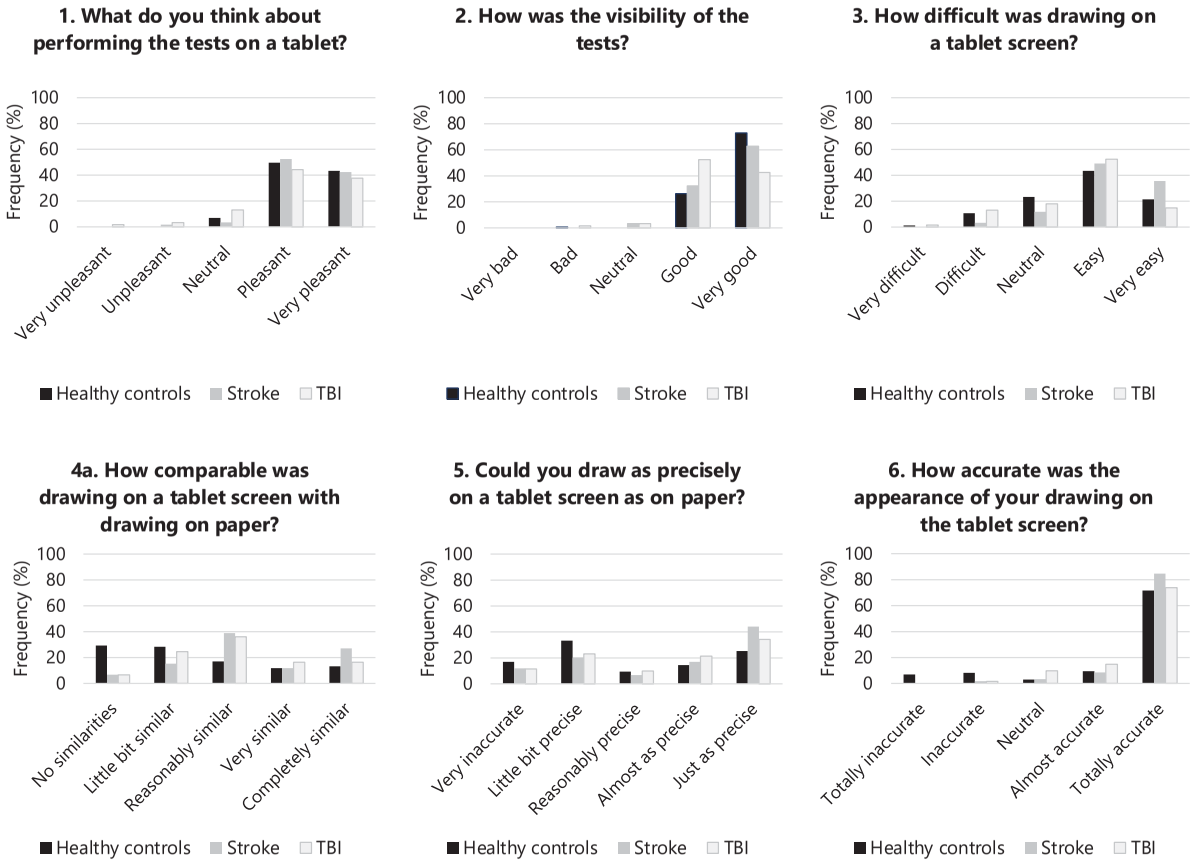

Figure 3.1. The six close-ended questions from the semi-structured interview are presented with the response options ranging from 1 (negative) to 5 (positive) with different labels for each question. The response options are presented on the horizontal axis. The frequency (%) of the reported response option is presented on the vertical axis, split per group.

(e.g., the surface of the tablet felt "more distant" compared to paper) (5%); and the hand position was different when using a pencil stylus and tablet (5%).

Patients and healthy controls suggested the following improvements to the digital administration: increasing the degree of friction of the surface of the screen or the pencil stylus (8%); adjusting the brightness of the tablet screen to individual needs (5%); and improving the quality of the audio fragments (5%) (e.g., to announce the start of a test to get used to the monotonous computerized voice, use human speech). Two-thirds of the participants (67%) was satisfied with the digital administration and did not suggest any improvements.

Applicability of conventional norms on digital tests

Three stroke patients had been assessed with a conventional NPA in the three months prior to participation and were excluded for these analyses to prevent potential practice effects influencing the current results (Calamia, Markon, & Tranel, 2012). Table 3.3 shows the percentages of stroke patients, TBI patients and healthy controls showing an abnormal performance (< 10^{th} percentile or below cut-off) on each outcome measure (see Appendix 3.3 for the average test scores and standard deviations per group). As expected, higher percentages of stroke and TBI patients performed abnormal on the tests when compared to healthy controls. Against expectations, more than 10% of the healthy controls showed abnormal performances on the RAVLT (immediate recall, delayed recall, recognition), TMT A, Clock Drawing, Cube Drawing, ROCF copy, Verbal Fluency Letter, Verbal Fluency Professions, WCST number of completed categories, and the WCST failure to maintain set.

Effect of tablet familiarity on test performance

With regard to the assumptions, no multicollinearity was examined, there was independence of observations, and no influential cases were identified. The scatter plots demonstrated linear relationships between the dependent and independent variables and homoscedasticity, except for the O-Cancellation, Star Cancellation, ROCF copy, WCST number of completed categories, and WCST failure to maintain set (see online Supplementary Figure 1ab). The p-p plots showed normally distributed standardized residuals, except for the O-Cancellation, Star Cancellation, Stroop 1, Stroop 2, WCST number of completed categories, and WCST failure to maintain set were cause for concern (see online Supplementary Figure 2ab).

Table 3.3. Percentages of patients and healthy controls showing an 'abnormal performance' based on Dutch conventional norms. Abnormal performance was defined as < 10th percentile or below cut-off for the RAVLT recognition, Cube Drawing, Clock Drawing, O-cancellation, Star Cancellation.

	Patients with stroke (*n* = 56)		**Patients with TBI** (*n* = 61)		**Healthy controls** (*n* = 159)	
Outcome measures	%	*n*	%	*n*	%	*n*
RAVLT Immediate recall	44.6	56	41.7	60	**33.8***	157
RAVLT Delayed recall	35.7	56	25.0	60	**22.9***	157
RAVLT Delayed recall corrected	7.1	56	11.7	60	6.4	157
RAVLT Recognition	12.5	56	16.7	60	**11.4***	157
TMT A	42.9	56	40.0	60	**24.5***	159
TMT B	19.6	56	26.7	60	3.1	159
TMT A-B	8.9	56	15.0	60	2.5	159
Clock Drawing	35.7	56	29.5	61	**25.8***	159
Cube Drawing	26.8	56	31.1	61	**22.6***	159
O-Cancellation	5.4	56	0.0	60	3.8	159
Star Cancellation	1.8	56	6.7	60	6.9	159
ROCF Copy	30.4	56	34.4	61	**16.4***	159
ROCF Immediate recall	12.7	55	18.0	61	8.8	159
ROCF Delayed recall	14.5	55	18.0	61	9.4	159
Verbal Fluency Letter	25.0	56	36.1	61	**15.1***	159
Verbal Fluency Animals	17.9	56	23.0	61	6.3	159
Verbal Fluency Professions	28.6	56	23.0	61	**10.1***	159
Digital Span	16.1	56	37.7	61	8.8	159
WCST Total errors	16.4	55	6.8	59	7.6	157
WCST Perseverative errors	9.1	55	6.8	59	4.5	157
WCST Non-perseverative errors	14.5	55	6.8	59	9.6	157
WCST Number of completed categories	16.4	55	16.9	59	**12.7***	157
WCST Failure to maintain set	22.2	54	18.6	59	**18.6***	156

Abbreviations: Rey Auditory Verbal Learning Test (RAVLT) Trail Making Test (TMT); Rey-Osterrieth Complex Figure (ROCF); Wisconsin Card Sorting Test (WCST). * More than 10% of the participants performing below 10th percentile or below cut-off (depicted **in bold**).

Significant effects of age, sex and level of education (model 1) were found on each outcome measure of the digital tests, except for the O-Cancellation (Table 3.4). There was no significant improvement in predicting the outcome measures of the digital tests when adding technological familiarity as new predictor (model 2). This finding suggests there was no significant effect of tablet familiarity on test performance on any of the outcome measures of the d-NPA.

Table 3.4. Results of the multiple regression analyses by using a hierarchical method based on the data of healthy controls

Outcome measures	**Model**	R^2	*F-change*	*Sig F-change*	*n*
RAVLT Immediate recall	Age, sex, education	.44	30.08	< .001	158
	Age, sex, education, tablet familiarity	.45	1.20	**.276**	
RAVLT Delayed recall	Age, sex, education	.39	24.66	< .001	158
	Age, sex, education, tablet familiarity	.40	0.73	**.394**	
RAVLT Recognition	Age, sex, education	.19	9.17	< .001	158
	Age, sex, education, tablet familiarity	.19	0.13	**.716**	
TMT A	Age, sex, education	.29	15.54	< .001	159
	Age, sex, education, tablet familiarity	.29	0.03	**.872**	
TMT B	Age, sex, education	.32	17.93	< .001	159
	Age, sex, education, tablet familiarity	.32	0.29	**.594**	
O-Cancellation	Age, sex, education	.04	1.38	.242	159
	Age, sex, education, tablet familiarity	.04	0.01	**.909**	
Star Cancellation	Age, sex, education	.08	3.10	.017	159
	Age, sex, education, tablet familiarity	.10	4.07	**.046**	
ROCF Copy	Age, sex, education	.14	6.45	< .001	159
	Age, sex, education, tablet familiarity	.17	5.13	**.025**	
ROCF Immediate recall	Age, sex, education	.21	9.92	< .001	159
	Age, sex, education, tablet familiarity	.22	2.23	**.137**	
ROCF Delayed recall	Age, sex, education	.26	13.82	< .001	159
	Age, sex, education, tablet familiarity	.27	1.17	**.282**	
Verbal Fluency Letter	Age, sex, education	.16	7.49	< .001	159
	Age, sex, education, tablet familiarity	.16	0.10	**.751**	
Verbal Fluency Animals	Age, sex, education	.16	7.40	< .001	159
	Age, sex, education, tablet familiarity	.17	0.67	**.413**	
Verbal Fluency Professions	Age, sex, education	.05	2.16	.076	159
	Age, sex, education, tablet familiarity	.05	0.14	**.714**	
Verbal Fluency Fruit/ furniture	Age, sex, education	.20	9.76	< .001	159
	Age, sex, education, tablet familiarity	.20	0.03	**.871**	
Digit Span	Age, sex, education	.21	10.12	< .001	159
	Age, sex, education, tablet familiarity	.21	0.50	**.479**	
Stroop 1	Age, sex, education	.09	3.64	.007	156
	Age, sex, education, tablet familiarity	.09	0.00	**.992**	
Stroop 2	Age, sex, education	.12	4.89	.001	154
	Age, sex, education, tablet familiarity	.12	0.01	**.941**	
Stroop 3	Age, sex, education	.24	11.81	< .001	153
	Age, sex, education, tablet familiarity	.24	0.39	**.532**	
WCST Total errors	Age, sex, education	.20	9.66	< .001	157
	Age, sex, education, tablet familiarity	.20	0.31	**.862**	

Table 3.4 continues on next page.

Table 3.4. *Continued*

Outcome measures	Model	R^2	*F-change*	*Sig F-change*	*n*
WCST Perseverative errors	Age, sex, education	.17	7.87	< .001	157
	Age, sex, education, tablet familiarity	.17	0.11	**.916**	
WCST Non-perseverative errors	Age, sex, education	.20	9.53	< .001	157
	Age, sex, education, tablet familiarity	.20	0.06	**.81**	
WCST Number of completed categories	Age, sex, education	.18	8.13	< .001	157
	Age, sex, education, tablet familiarity	.18	0.11	**.737**	
WCST Failure to maintain set	Age, sex, education	.11	4.65	< .001	157
	Age, sex, education, tablet familiarity	.11	0.36	**.551**	

Note. *F-change* represents the improvement in predicting the outcome measure by adding a new predictor to the model. We evaluated whether this change was significant (*Sig F-change*; **in bold**). Based on a Benjamini Hochberg correction, there was no significant improvement.

Discussion

In this study, we investigated (1) the feasibility and user-experience of a d-NPA in patients with ABI and healthy controls; (2) the applicability of conventional norms on digital tests, and (3) whether familiarity with a tablet would affect test performance on a tablet. We found that the administration of a d-NPA seems feasible for cognitive assessment in patients with ABI. The digital administration was considered a pleasant experience for patients with ABI and healthy controls. Only 6% of the patients was unable to complete the d-NPA, 5% needed an extra break, and 6% needed an adjustment of the brightness and/or volume. Patients who did not complete the d-NPA reported mental fatigue or sensory overload caused by an overdose of stimuli and/or the brightness of the tablet screen. As we did not directly compare the d-NPA with a conventional NPA, we cannot rule out the possibility that these patients would have experienced sensory overload with paper-and-pencil tests as well, as sensory overload may be caused by various factors (e.g., task demand, fatigue) (Scheydt et al., 2017). The brightness of the tablet screen, however, may add to the sensory overload and adjusting brightness might be a proper solution to suit individual needs. However, brightness and/or luminance contrast can have an impact on the readability or visibility of visual stimuli (Schlegel & Gilliland, 2007), so future research should investigate how adjustments in brightness and contrast impacts test performance and develop adapted norms for brightness and/or contrast levels, when this may affect performance.

The conventional paper-and-pencil norms were not applicable for half of the digital tests, as up to 34% of healthy controls showed an abnormal performance (< 10^{th} percentile or below cut-off) (Lezak et al., 2012). There are several possible explanations for this result. An explanation may be the subtle – but relevant – differences in administration (paper-

and-pencil vs. tablet-and-pencil stylus) that might have influenced test performance. For instance, patients and healthy controls reported that the tablet screen gave less friction when drawing with the pencil stylus. Due to low friction, people tend to draw faster on a tablet than with pencil on a paper (Gerth et al., 2016; Guilbert, Alamargot, & Morin, 2019), which might result in an unprecise drawing (see Figure 3.2 with the ROCF as an example). Furthermore, the quality of the speech synthesizer (i.e., artificial production of human speech) may have influenced the clarity. In especially the RAVLT, it may therefore have been difficult to correctly identify the words. Finally, changes in the nature of a response and feedback may also affect test performances (Schlegel & Gilliland, 2007). For instance in the WCST, virtual cards were displayed on the tablet (instead of the use of real cards), and the participant received written feedback (instead of verbal feedback). Previous studies reported that normative data that exists for paper-and-pencil tests cannot simply be applied to digital tests, as performances on paper-and-pencil and digital tests are not directly comparable (Bauer et al., 2012; Germine et al., 2019; Parsey & Schmitter-Edgecombe, 2013). For this reason, even when a digital test mirrors a paper-and-pencil test, new clinical norms are needed (Bauer et al., 2012).

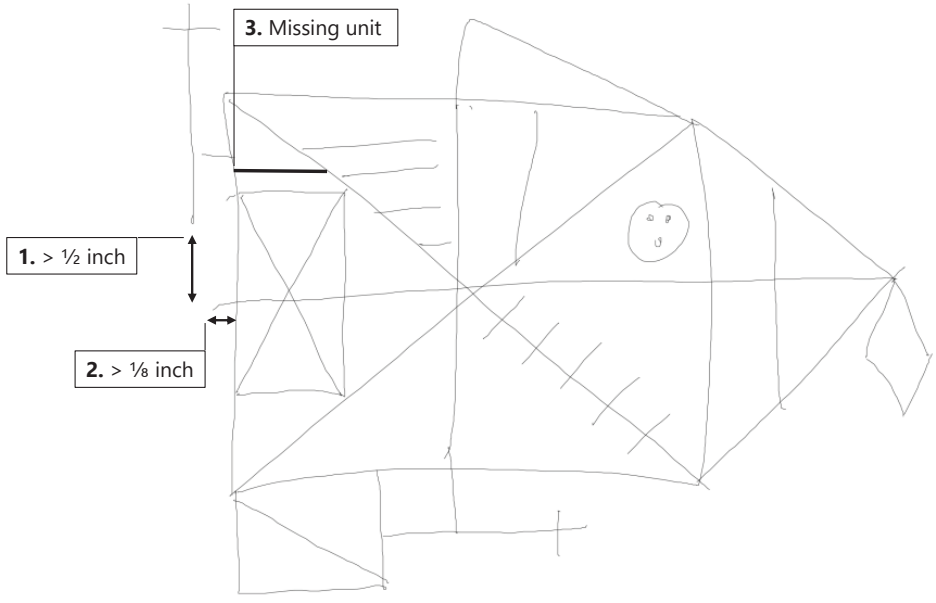

Figure 3.2. Example of a copy of the Rey-Osterrieth Complex Figure performed by a healthy control (30 years of age) with a total score of 32. Even though most units were present, unprecise drawing (highlighted in the example) resulted in a weak performance. For instance, (1) the height of the vertical cross should not extend more than ½ inch above the horizontal line (minus 1 point); (2) The horizontal line should not overshoot the vertical segments of the large rectangle more than 0.5 inch (minus 1 point); and (3) a horizontal line should be drawn parallel to and directly above the small rectangle (minus 2 points) (Meyers & Meyers, 1995).

Another important factor might regard the characteristics of the conventional norms used in this study. Norms are ideally updated regularly (Germine et al., 2019). However, many paper-and-pencil tests exist for decades and test performances are interpreted using norms from studies that were conducted several decades ago (in this study ranging from the year 1993-2012) (Bilder & Reise, 2019; Dickinson & Hiscock, 2011). General experiences of a population change over time and highly affect test performance, also known as the Flynn effect (Dickinson & Hiscock, 2011). The Flynn effect refers to the rise of scores on intelligence and neuropsychological tests throughout the 20th century. In contrast to the Flynn effect, a surprisingly high number (26%) of healthy participants were not able to draw a clock correctly. Participants placed the numbers outside the contour or even placed the hands incorrectly, which is unlikely a result of differences in the means of assessment (paper-and-pencil vs. tablet-and-pencil stylus). Environmental changes resulting from modernization – such as greater use of technology – might result in the fact that people are increasingly accustomed to digital clocks. Previous studies have described concerns regarding the long-term use of the clock-drawing test due to the advent of digital clocks (Hazan, Frankenburg, Brenkel, & Shulman, 2017; Shulman, 2000). Furthermore, normative data that derived from a specific population may not be generalizable to different populations (Lezak et al., 2004), which may result in false positives or negatives (see Appendix 3.2 for the normative population characteristics). In short, developing and regularly updating clinical norms is crucial in neuropsychological assessment (Dickinson & Hiscock, 2011; Germine et al., 2019) and should be taken into account in order to implement a d-NPA in clinical practice.

Results on previous studies suggested that people with greater computer experience tend to perform better on computerized tests than those with less computer experience (Iverson et al., 2009; Tun & Lachman, 2010). Here, familiarity with a tablet did not affect cognitive test performances. This finding is consistent with a recent study of Wallace et al. (2019), who also found no differences in test performances between TBI patients who reported to be less or more comfortable with an iPad (Wallace et al., 2019). Touch-screen devices require little training, little cognitive demands, and little hand-eye coordination and are therefore easy to use, even by individuals who are minimally exposed to technology (Canini et al., 2014; Cernich et al., 2007; Holzinger, 2010; Wood, Willoughby, Rushing, Bechtel, & Gilbert, 2005). Therefore, in d-NPA, tablets should be chosen over computers with keyboard, computer mouse or joystick.

Strength and limitations

An important strength of this study was the engagement of a large number of stroke and TBI patients (n = 120). The importance of including end users in the development and evaluation

of new medical technological devices is more and more acknowledged and stressed (Jenkins et al., 2016; Shah & Robinson, 2007). We intentionally aimed for a large and heterogeneous sample of patients to increase its representativeness. A general concern might regard a potential selection bias, where patients who are willing to participate are probably patients who are less impaired (Knudsen, Hotopf, Skogen, Øverland, & Mykletun, 2010; Olson, Parkinson, & McKenzie, 2010). Our patient samples were relatively young and moderately impaired, which might be regarded as a limitation since we cannot generalise the current findings to an older and/or more impaired population. We suspect that a d-NPA might be a bit more challenging with an older population and/or a more impaired population, just like the conventional NPA would be. As such, there is no indication that the d-NPA would not be feasible for other groups, yet this remains to be tested.

One potential limitation is that injury characteristics were not systematically noted in the medical files, and we were therefore unable to further investigate specific subgroups within the patient samples. For example, it would have been interesting to investigate whether lesion location, volume, severity of stroke or TBI determined by classification measures (e.g., the Glasgow Coma Scale, duration loss of consciousness or post-traumatic amnesia) would affect the feasibility or user-experience. With the current results, where the majority of the patients (94%) were able to complete the d-NPA and considered it as "pleasant", there is no direct reason to assume that there would be very large deviations within specific subgroups.

One might argue that the design of the study is not ideal, as we did not directly compare a paper-and-pencil and a digital administration. Even though we did not aim for a direct comparison, we do feel that we need to address this alternative design. When one would be interested in examining differences between a paper-and-pencil and a digital administration with respect to user-experience and test performances, participants would need to be assessed twice with the same tests. A long duration between sessions would be necessary as otherwise mainly practice effects would be assessed (Calamia et al., 2012). In general, diminishing or removing practice effects is challenging when using a within-subjects design in neuropsychological research. For this reason, we investigated the feasibility and user-experience of a d-NPA, without the direct comparison with a conventional NPA.

Finally, there are two drawbacks in the current study. First, the average age of healthy controls was significantly higher compared to the patient groups. Conventional norms, however, correct for the effect of age on test performances, and as such the current results – corrected for age – still hold. Second, we used self-report to measure tablet familiarity, as we asked participants to estimate how many hours per week they use a tablet. It is generally accepted that the validity of retrospective self-reports may be compromised, due to for

example a limited autobiographical memory (Schwarz, 2007). Even though tablet familiarity did not seem to have an important effect on test performance, alternative measures would have possibly been more suitable, such as measures capturing real-time data (e.g., diaries, applications that register how much time people spend on a tablet).

Future research

Based on our findings, researchers and manufacturers should collaborate to reduce potential restrictions for optimal use (e.g., low friction of tablet screens, low quality of speech synthesizer) that interfere with the user-experience and usability of such devices. A d-NPA offers several advantages over a paper-and-pencil assessment, such as a more standardized administration with an increased accuracy and timing of stimulus presentation. A d-NPA allows an automatized scoring which saves valuable professional time and is less prone to human errors. In addition, manual and verbal responses can be replayed afterwards, avoiding observations or order of responses to be lost. Moreover, a digital response acquisition allows for a highly precise and detailed data collection, which opens the possibility to develop novel outcome measures to assess subtle cognitive impairments (Davis, Libon, Au, Pitman, & Penney, 2014; Diaz-Orueta, Blanco-Campal, Lamar, Libon, & Burke, 2020; Parsey & Schmitter-Edgecombe, 2013). A next step should be the development of additional outcome measures that go beyond the traditional outcome measures of paper-and-pencil tests. Accurate time measures could reveal fluctuations in test performance (Spreij et al., n.d.), and algorithms could improve the assessment of the process of construction in drawing tests (Kim, Cho, & Do, 2011). Finally, the development of new norms remains crucial in order to implement a d-NPA in clinical practice (Germine et al., 2019).

Conclusions

The administration of a d-NPA is feasible in patients with ABI. The digital administration was considered a pleasant experience for patients with ABI and healthy controls. Familiarity with a tablet did not impact test performance, which is particularly important in neuropsychological assessment. Conventional norms that exist for the paper-and-pencil tests were not applicable on the digital version of the tests. Future research should focus on developing norms in order to implement a d-NPA in clinical practice.

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Appendix 3.1. Overview of developed computerized test batteries

Test battery	Type of tests	Response device	Supervision	Reference and website
Automated Neuropsychological Assessment Metrics (ANAM)	New tests	Mouse and keyboard	Self-administration	(Kabat, Kane, Jefferson, & DiPino, 2001; Kane & Reeves, 1997) www.vistalifesciences.com
Cambridge Neuropsychological Test Automated Battery (CANTAB)	New tests	Touch-screen device	Self-administration	(Robbins et al., 1998, 1994) www.cambridgecognition.com/cantab
National Institutes of Health Toolbox (NIH Toolbox)	New tests	Touch-screen device (iPad)	Examiner	(Gershon et al., 2010) www.nihtoolbox.org
Computerized Neurocognitive Testing Vital Signs (CNSVS)	Computerized version of conventional tests	Keyboard keys	Self-administration	(Gualtieri & Johnson, 2006) www.cnsvs.com
Micro-Cog Assessment of Cognitive Functioning (MicroCog)	New tests	Keyboard keys	Self-administration	(Elwood, 2001; Powell, Kaplan, Whitla, Catlin, & Funkenstein, 1993)
Neurobehavioral Evaluation System (from the National Institute of Health) (NES)	New tests	Keyboard keys and a joystick	Self-administration	(Baker et al., 1985)
IntegNeuro	New tests	Touch-screen and voice recording software	Self-administration	(Paul et al., 2005) www.brainclinics.com/solutions
WebNeuro	New tests	Computer and keyboard	Self-administration	(Silverstein et al., 2007) www.totalbrain.com
FePsy	Combination of conventional and new tests	Computer or touch-screen	Examiner	www.fepsy.com

Appendix 3.1. *Continued*

Test battery	Type of tests	Response device	Supervision	Reference and website
Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)	New tests	Microcomputer	Minimal supervision by an examiner	(Maroon et al., 2000) www.impactconcussion.com
Metrisquare DiagnoseIS	Combination of conventional and new tests	Tablet and pencil stylus	Examiner	www.metrisquare.com
Vienna Test System	Combination of conventional and new tests	Response panel with keys, buttons, joysticks, and foot pedals, and for some tests a touch-screen	Examiner	(Shuhfried, 2013) www.schuhfried.com/vts
Pearson's Q-interactive platform	Computerized version of conventional tests	Touch-screen device (iPad)	Examiner	www.pearsonassessments.com/professional-assessments/digital-solutions/q-interactive

Appendix 3.2. Details of digital neuropsychological assessment

Tests	Outcome measures	Reference stimuli, instructions and scoring	Reference Dutch normative data	Normative population characteristics (*n*; male (%); age; education; nationality)
Rey Auditory Verbal Learning Test	Immediate recall: correct recalled words (0–75) Delayed recall: correct recalled words (0–15) Delayed recall corrected: corrected for total recalled words Recognition: correct recognized words (0–30)	Stimuli were based on wordlist A (Saan & Deelman, 1986). Instructions (translated to Dutch) and scoring (Strauss, Sherman, & Spreen, 2006).	(Schmand et al., 2012)	*n* = 847; 45%; 14–87y; mdn = 5 (Verhage); Dutch
Trail Making Test	Completion time part A (seconds) Completion time part B (seconds) Completion time part A-B (seconds)	Stimuli (Reitan, 1955); Instructions (adapted to a digital administration) and scoring (Strauss et al., 2006).	(Schmand et al., 2012)	*n* = 478; 42%; 17–90y; mdn = 5 (Verhage); Dutch
Clock	Correct drawn units (contour, numbers, hands) (0–3)	Instructions and scoring (Nasreddine et al., 2005).	(Nasreddine et al., 2005)	*n* = 90; 46%; mean 72.8y; mean = 13.3y; Canadian
Cube	Correct drawn elements (3D, parallel, missing and extra lines) (0–1)	Instructions and scoring (Nasreddine et al., 2005).	(Nasreddine et al., 2005)	*n* = 90; 46%; mean 72.8y; mean = 13.3y; Canadian
O-Cancellation	Difference in number of omissions between left and right side (0–20)	Stimuli, instruction and scoring (Rasquin, Ooms, van de Sande, Beers, & Schmand, 2009).	≥ 2	*n* = 39; Dutch
Star Cancellation	Difference in number of omissions between left and right side (0–27)	Stimuli, instruction and scoring (Wilson, Cockburn, & Halligan, 1987).	(Van der Stoep et al., 2013)	*n* = 28; 57%; mean 42.3y; n.a.; Dutch
Rey-Osterrieth Complex Figure	Copy: correct drawn units (0–36) Immediate recall: correct drawn units (0–36) Delayed recall: correct drawn units (0–36)	Stimuli, instruction, and scoring (Meyers & Meyers, 1995).	(Meyers & Meyers, 1995)	*n* = 601; 18–89y; n.a.; American
Verbal Fluency - Letter	Letters used (D-A-T): Total correct produced words	Instruction and scoring (Schmand, Groenink, & Van Den Dungen, 2008).	(Schmand et al., 2012)	*n* = 570; 41%; 17–90y; mdn = 5 (Verhage); Dutch

Appendix 3.2. *Continued*

Tests	Outcome measures	Reference stimuli, instructions and scoring	Reference Dutch normative data	Normative population characteristics (*n*; male (%); age; education; nationality)
Verbal Fluency - Category	Animals: correct produced words Professions: correct produced words Fruit and furniture (switch): correct produced words	Stimuli, instruction and scoring (Schmand et al., 2008).	(Schmand et al., 2012) (Schmand et al., 2012) Not available	Animals: *n* = 463; 41%; 17–90y; mdn = 5 (Verhage); Dutch Professions: *n* = 394; 61%; 17–90y; mdn = 5 (Verhage); Dutch
Digit Span	Number of correct recalled sequences (16 forward; 14 backward)	Stimuli were based on the right column (version B) of random digits (Lezak, 2004). Instructions and scoring (Lezak et al., 2004).	(Wechler, 2004)	*n* = 2250; 50–68%; 16–89y; 8–16y; American
Stroop	Completion time condition 1 (seconds) Completion time condition 2 (seconds) Completion time condition 3 (seconds) Completion time condition 3-2 (seconds)	Stimuli were based on the Stroop test version, but with a different order (Hammes, 1973): (1) all colours occur an equal number of times, (2) adjacent colours are never the same (so no red-red), (3) all colours appear in each row, (4) the sequence is different for each card. Instructions and scoring (Strauss et al., 2006).	Dutch clinical norms did not correspond with the used stimuli of the digital version of the Stroop.	N.A.
Wisconsin Card Sorting Test*	Total errors (0–128) Perseverative errors (0–128) Non-perseverative errors (0–128) Number of completed categories (0–6) Failure to maintain set (0–6)	Stimuli were based on Heaton's version (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), but another order was used. Instructions and scoring (Heaton et al., 1993).	(Heaton et al., 1993)	*n* = 445; 49%; 18–89y; 6–20y; American

Abbreviations: years (y); median (mdn). * Most frequently used outcome measures (Nyhus & Barceló, 2009).

Appendix 3.3. Average test scores and standard deviations per group

	Patients with stroke (*n* = 56)		**Patients with TBI** (*n* = 61)		**Healthy controls** (*n* = 159)	
Outcome measures	mean (*SD*)	*n*	mean (*SD*)	*n*	mean (*SD*)	*n*
RAVLT Immediate recall (0–75)	38.32 (11.41)	56	43.55 (12.94)	60	41.12 (11.69)	158
RAVLT Delayed recall (0–15)	7.98 (3.46)	56	9.28 (3.53)	60	8.65 (3.50)	158
RAVLT Recognition (0–30)	28.13 (2.15)	56	28.65 (2.04)	60	28.73 (1.68)	158
TMT A (time in seconds)	45.48 (21.66)	56	41.98 (19.43)	60	41.46 (16.65)	159
TMT B (time in seconds)	95.47 (61.60)	56	87.78 (44.86)	60	74.83 (26.96)	159
TMT A-B (time in seconds)	50.00 (47.65)	56	45.81 (36.13)	60	33.38 (20.77)	159
Clock Drawing (0–3)	2.57 (0.63)	56	2.62 (0.64)	61	2.70 (0.55)	159
Cube Drawing (% correct)	73.2	56	68.9	61	77.4	159
O-Cancellation (0–20)	0.37 (0.70)	56	0.20 (0.40)	60	0.25 (0.54)	159
Star Cancellation (0–27)	0.30 (0.50)	56	0.30 (0.77)	60	0.43 (0.73)	159
ROCF Copy (0–36)	32.43 (3.44)	55	32.25 (3.26)	61	32.67 (2.93)	159
ROCF Immediate recall (0–36)	17.86 (6.19)	55	19.57 (6.56)	61	19.03 (6.32)	159
ROCF Delayed recall (0–36)	17.97 (5.89)	55	19.51 (6.48)	61	19.12 (6.04)	159
Verbal Fluency Letter (produced words)	32.29 (8.41)	56	31.20 (10.73)	61	37.92 (11.4)	159
Verbal Fluency Animals (produced words)	21.95 (5.99)	56	22.02 (5.82)	61	25.24 (6.10)	159
Verbal Fluency Professions (produced words)	15.88 (5.34)	56	16.46 (4.72)	61	18.74 (5.25)	159
Digital Span (0–30)	12.32 (3.33)	56	11.75 (4.03)	61	13.51 (3.38)	159
WCST Total errors (0–128)	33.15 (19.88)	55	24.86 (17.76)	59	26.86 (20.24)	157
WCST Perseverative errors (0–128)	17.20 (12.84)	55	12.66 (11.25)	59	13.76 (12.34)	157
WCST Non-perseverative errors (0–128)	15.95 (9.0)	55	12.20 (7.59)	59	13.10 (9.19)	157
WCST Number of completed categories (0–6)	4.65 (1.87)	55	5.15 (1.51)	59	4.90 (1.83)	157
WCST Failure to maintain set (0–6)	1.58 (1.50)	54	1.29 (1.55)	59	1.38 (1.60)	157

Abbreviations*:* Standard deviation (SD); Rey Auditory Verbal Learning Test (RAVLT) Trail Making Test (TMT); Rey-Osterrieth Complex Figure (ROCF); Wisconsin Card Sorting Test (WCST).

On Friday the 13th, in May 2016, I suffered from a stroke and was taken to the hospital by an ambulance. I suffered from a second stroke in the ambulance, which was frightening for my husband. The medical doctors told me I had two minor strokes. Since the strokes, the right side of my body feels numb, even though I can move and do everything. Mentally, I feel like a mess. At first glance, people don't notice the changes, but I can only focus for about 45 minutes. After that, I lose my concentration and even have difficulties making conversation. I am so terribly tired that I need to sleep for 2 hours. During my rehabilitation trajectory, they administered a neuropsychological assessment and I did relatively well. A neuropsychological assessment is useful to assess cognitive disorders. However if no clear disorders are found, it fails to predict how a person functions in daily life. The employee insurance agency and the occupational health service attach great importance to the results, but it also matters how you feel during the assessment and the day after. I can still do everything, but I can only do it for a little while. I often explain it as "muscular soreness after physical exercise". If I put a lot of effort in a mental activity, I feel the consequences up to two days later. Because of my pharmaceutical background, I know the necessity to participate in studies to move research forward and expand the knowledge about brain injuries and its consequences.

Chapter 4

The journey is just as important as the destination – Digital neuropsychological assessment provides performance stability measures

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Abstract

Background: Cognitive performances on neuropsychological paper-and-pencil tests are in general evaluated quantitively by examining a final score (e.g., total duration). Digital tests allow for a quantitative evaluation of "how" a patient attained a final score, which opens the possibility to assess more subtle cognitive impairment even when final scores are evaluated as normal. We assessed performance stability (i.e., the number of fluctuations in test performance) to investigate (1) differences in performance stability between patients with acquired brain injury (ABI) and healthy controls; (2) the added value of performance stability measures in patients with ABI; and (3) the relation between performance stability and cognitive complaints in daily life in patients with ABI.

Methods: We administered three digital neuropsychological tests (Rey Auditory Verbal Learning Test, Trail Making Test, Stroop Colour and Word Test) and the Cognitive Complaints - Participation (CoCo-P) inventory in patients with ABI (n = 161) and healthy controls (n = 91).

Results: Patients with ABI fluctuated more in their performance on all tests, when compared to healthy controls. Furthermore, 4–15% of patients who performed inside normal range on the conventional final scores were outside normal range on the performance stability measures. The performance stability measures, nor the conventional final scores, were associated with cognitive complaints in daily life.

Conclusions: Stability in test performance of patients was clearly dissociable from healthy controls, and may assess additional cognitive weaknesses which might not be observed or objectified with paper-and-pencil tests. More research is needed for developing measures better associated with cognitive complaints.

Introduction

Neuropsychological paper-and-pencil tests are widely used to assess cognitive impairment (Harvey, 2012; Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006; Vakil, 2012). Performances on these tests are usually scored by examining a final score, such as the total duration, number of correct responses, or a final drawing (Diaz-Orueta, Blanco-Campal, Lamar, Libon, & Burke, 2020). A well-known issue in neuropsychological assessment is the discrepancy between "normal" final scores and the difficulties patients encounters in daily life (Bielak, Hatt, & Diehl, 2017; Chaytor & Schmitter-Edgecombe, 2003). An important turning point in neuropsychological assessment was the development of what is now referred to as the "Boston Process Approach" (Kaplan, 1988). This method focusses by close observation, on the qualitative analyses of errors and the "process" or the means by which a patient attains a final outcome. Capturing and evaluating the process opens the possibility to assess more subtle cognitive impairment even when final scores are evaluated as normal (Davis, Libon, Au, Pitman, & Penney, 2014; Diaz-Orueta et al., 2020; Kim, Cho, & Do, 2010).

A major concern of the qualitative analysis of the process is on its inter-rater reliability as differences in outcome may occur between administrators. In addition, determining an abnormal performance (i.e., outside normal range based on performances of healthy controls) remain challenging based on a qualitative analysis. Digital tests allow a highly detailed registration of data, which enables the development of *quantitative* measures of "how" a patient attained a final outcome. In this study, we capitalized the opportunities afforded by digital tests and developed novel outcome measures to assess more subtle cognitive impairment. We assessed *performance stability* by using three digital neuropsychological tests, namely the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT) and the Stroop Colour and Word Test (Stroop). Performance stability is defined as the number of fluctuations in pace (e.g., naming speed in the RAVLT, drawing speed in the TMT). Individuals may show a low stability in test performance, when they respond in an inconsistent pace, outside the normal range based on healthy controls. A low stability in test performance might suggest that underlying processes, such as fluctuating attention or cognitive effort, affect cognitive function negatively (Milberg, Hebben, & Kaplan, 1986). We hypothesized that we would find differences in performance stability between patients with acquired brain injury (ABI) and healthy controls, and that performance stability measures would be of added value in detecting (subtle) cognitive weaknesses in reference to conventional final scores. Furthermore, neuropsychological tests are often not sensitive enough to assess mild cognitive impairment that might only be noticed in daily life situations (Chaytor & Schmitter-Edgecombe, 2003; Spooner & Pachana, 2006). In this study, we

describe a first attempt to develop more sensitive measures that might better correspond to difficulties patients encounter in daily life. We explored whether a low stability in test performance would correspond to reported cognitive complaints during daily life activities.

To summarize, we investigated (1) differences in performance stability between patients with acquired brain injury (ABI) and healthy controls; (2) the added value of performance stability measures for patients with ABI only, in reference to conventional final scores; and (3) the relation between performance stability and cognitive complaints in daily life for patients with ABI.

Materials and methods

Participants

Participants in this study derived from separate studies in which a digital neuropsychological assessment (d-NPA) was administered. A subset of participants was also part of another study investigating a newly-developed questionnaire assessing cognitive complaints in daily life. All participants gave written informed consent. The experiments were performed in accordance with the Declaration of Helsinki. The research protocols were approved by the Medical Ethics Committee of University Medical Centre Utrecht (METC protocol numbers 16-760/C, 17-407/C, 19-112/C).

We recruited patients with ABI based on the following inclusion criteria: (1) clinically diagnosed with stroke or brain tumour as indicated by clinical computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinically diagnosed with traumatic brain injury as indicated by a neurologist; (2) aged ≥ 18 years; (3) fluent in Dutch; (4) patients lived at home at the time of participation; (5) no conventional NPA for clinical purposes in the coming or past three months. Patients were directly invited by clinicians or via an information brochure that was sent by post. The information brochure was also shared with patient associations and on social media. For patients who were willing to participate an appointment was scheduled at the *Department of Rehabilitation* at *University Medical Centre Utrecht*, *De Hoogstraat Rehabilitation Centre*, or at a patient's home.

We recruited healthy controls based on the following inclusion criteria: (1) no medical history of neurological and/or psychiatric disorders for which medical treatment was necessary; (2) aged ≥ 18 years; and (3) fluent in Dutch. Healthy controls were recruited among colleagues and acquaintances, or via an information brochure shared with (sport) associations, or on social media.

Digital Neuropsychological Assessment (d-NPA)

Materials

The d-NPA was administered by a neuropsychologist so no behavioural observations would be lost. The d-NPA contained twelve digital tests administered in a fixed order (Spreij, Gosselt, Visser-Meily, & Nijboer, 2020). Data of only three tests were included in this study: RAVLT, TMT and the Stroop. The software of the d-NPA was a research prototype created by Philips Research (Vermeent et al., 2020). A tablet was placed in front of the participant and the neuropsychologist sat across them while controlling the tests on a regular laptop. The tablet (Apple© iPad Pro) had a screen size of 12.9-inch and a screen resolution of 2732 × 2048 pixels, and participants used a pencil stylus (Apple© Pencil) which functioned as an ordinary ballpoint pen.

Digital tests and conventional outcome measures

Rey Auditory Verbal Learning Test (RAVLT)

Participants were required to recall as many words as possible from a list of fifteen words played on the laptop (volume was set on 100%). This procedure was repeated five times (immediate recall). Subsequently, participants were required to recall the words after 10–20 minutes (delayed recall). The correctly recalled words were used as conventional final scores (immediate recall [0–75] and delayed recall [0–15]).

Trail Making Test (TMT)

Participants were required to 'connect-the-dots' of 25 consecutive targets with the pencil stylus on the tablet. There were two parts to the task: (a) all targets were numbers (1, 2, 3, etc.) and participants were required to connect them in a sequential order; and (b) targets were numbers and letters and patients were required to alternate between numbers and letters (1, A, 2, B, etc.). Time of completion for both parts separately were used as conventional final score.

Stroop Colour and Word Test (Stroop)

In three conditions, items (colour blocks, colour words in black ink, colour words in colour ink) were arranged in a matrix of 10 × 10 columns and rows and presented on the tablet. Participants were required to (1) name the colour of the blocks; (2) read the colour word; and (3) name the colour of the ink as fast as possible. The time of completion per condition was used as conventional final score.

Measures of performance stability

The timing of each response was captured, due to an automatic time-stamped data collection. Manual responses (TMT) derived from pen strokes on the tablet screen and were composed in time-stamped coordinates. Pen strokes were classified by being within or outside a target (i.e., circle). Verbal responses (RAVLT, Stroop) were time-based logged by a neuropsychologist by typing the response during the test administration.

In the data pre-processing stage, raw files were read and processed with Python 3.7 (Python Core Team., 2020). See Appendix 4.1 for a detailed explanation of the development of performance stability measures and the documentation of missing data analyses. In short, a similar approach was adopted for all three tests (RAVLT, TMT and Stroop) to compute performance stability. First, we determined a time-based measure specific for each test (e.g., time between responses for the Stroop, as indication of "naming speed"). Second, we defined the number of time bins for each test condition (e.g., 10 time bins of 10 words in the Stroop [100 words in total]). The standard error – as measure of variability – was calculated per time bin. We defined a normal range as a 95% Confidence Interval (95%CI) based on the standard errors of the healthy controls, by using the arithmetic mean and standard error of the mean. Next, the standard error was calculated per time bin for each individual patient, and was categorized as below, above or within the normal range of standard errors found in healthy controls. Finally, the number of time bins in which the standard error of a patient fell above normal range (e.g., 7 out of 10 bins) was computed this into a proportion score (e.g., .7). This score reflected *performance stability* (range 0–1), with a higher score indicating a higher number of fluctuations in test performance. See Figure 4.1 for a visualization of the development of the performance stability measures.

Cognitive Complaints – Participation (CoCo-P)

Participants were instructed to fill-out the CoCo-P at home and return them by post. The CoCo-P is a patient-reported measure to assess cognitive complaints during daily life activities (Spreij, Sluiter, Gosselt, Visser-Meily, & Nijboer, 2019). The CoCo-P contains 38 items focusing on memory (i.e., retrospective memory, prospective memory), attention (i.e., arousal, orienting, monitoring, sustained) or executive function (i.e., planning, self-evaluating, initiative, mental flexibility) divided over 10 daily life activities (i.e., work/education, leisure activities, travel, driving, finances, use of medication, family life, contact with family, friends and community, cooking, grocery shopping). The response options reflect different grades of independence and effort (0 [independently without effort], 1 [independently with effort], 2 [with help], 3 [not possible], 4 [not applicable]). We computed a *complaint score* per cognitive domain with the following formula: $complaints\ score = \frac{mean\ score}{3} \times 100$. Only items that were applicable for the participant were included. Higher scores indicated a higher degree of reported complaints.

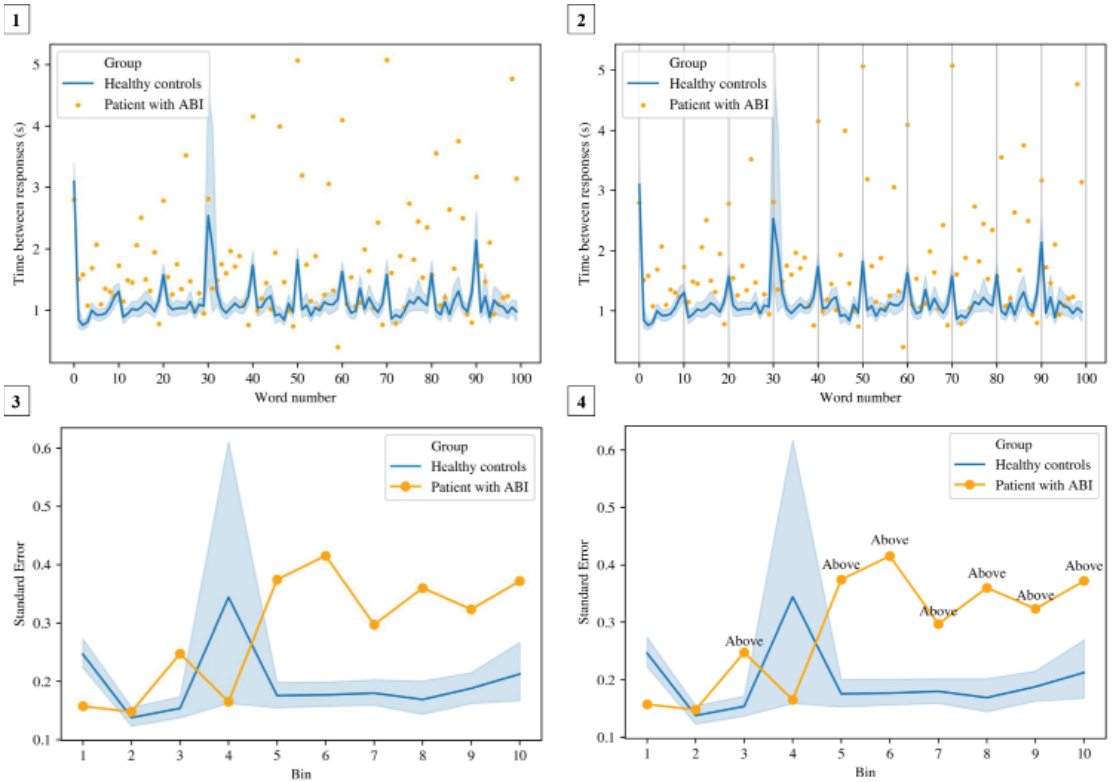

Figure 4.1. The development of the performance stability measures. The development (in this example the Stroop, condition 3) is illustrated for one patient in four steps: **(1)** The "time between responses" (in seconds) is depicted on the vertical axis, with the orange dots reflecting the time between responses for one patient. The words (100 words in total) are depicted on the horizontal axis. The blue line is the average time of the healthy controls (n = 91) with a 95%CI (light blue shade); **(2)** In the Stroop, we computed 10 time bins of 10 words each. The standard error was calculated per time bin; **(3)** Here, the 10 time bins are depicted on the horizontal axis, and the standard error on the vertical axis. The orange line represents the standard error per time bin for one patient. **(4)** The number of time bins in which the standard error of a patient fell above normal range (e.g., 7 out of 10 bins) was computed into a proportion score (e.g., .7).

Demographic and clinical characteristics

We collected data on sex, age and level of education. Level of education was assessed by using a Dutch classification system (Verhage, 1965), that consists of seven ranks, with 1 being the lowest (less than primary school) and 7 being the highest (academic degree). These levels were converted into three categories for analysis: low (Verhage 1–4), average (Verhage 5), and high (Verhage 6–7). The Mini-Mental State Examination – 2nd edition (MMSE-2) was administered as indication of general cognitive functioning (Folstein, Folstein, White, & Messer, 2010). In addition, we extracted the following clinical characteristics from the medical files: ABI type, time post ABI onset, and lesion side.

Statistical analysis

Demographic and clinical characteristics

Non-parametric tests (Mann-Whitney *U* test for continuous variables and Chi-square test for categorical variables) were used to compare demographic and clinical characteristics between patients with ABI and healthy controls.

Differences in performance stability between patients with ABI and healthy controls

We first presented the results on group level by comparing the *standard error* per stage, time bin, and group for each determined outcome measure per test (RAVLT [in time between responses], Stroop [time between responses], and TMT [time spent within target; drawing speed]). A repeated measures analysis of variance (ANOVA) was performed with stage and time bin (number of stages and time bins varied per test; see Appendix 4.1) as within-subjects variables, and with group (patients with ABI versus healthy controls) as between-subjects variable. We reported the partial eta-squared (η^2) as effect size, with > .01 reflecting a small effect, > .06, a medium effect, and > .14 a large effect (Cohen, Miles, & Shevlin, 2001).

Several assumptions were evaluated as followed: (1) the distribution of the dependent variable (standard error per stage and time bin) in the two groups was measured with a Shapiro-Wilk normality test. Wherever normality was violated, we evaluated whether outliers influenced the overall results by using Cook's distances. If there were no influential outliers, no transformation was computed as repeated measure ANOVA is claimed to be more robust to violations of assumptions of normality; (2) sphericity – variances of the differences between all combination – was measured with a Mauchly's Test. Wherever sphericity was violated, a Greenhouse-Geisser correction was applied.

Added value of performance stability measures in reference to conventional final scores

For each test, we calculated the added value of performance stability measures, in reference to the conventional final scores, by determining the percentage of patients who performed inside normal range based on the final scores, but outside normal range based on the performance stability measures. For the performance stability measures, we determined a cut-off based on 2 standard deviations above the average score of healthy controls. Since conventional norms that exist for paper-and-pencil tests cannot be applied on digital versions of the tests (Bauer et al., 2012; Germine, Reinecke, & Chaytor, 2019; Parsey & Schmitter-Edgecombe, 2013; Spreij et al., 2020), we computed percentiles based on healthy controls for each conventional final score to determine a cut-off. A score below 5th percentile was indicative as abnormal performance (see Appendix 4.1 for the cut-off scores).

Relation between final scores, performance stability and cognitive complaints in daily life

Within patients with ABI only, we computed non-parametric spearman correlations the performance stability measures and the complaints score, and the conventional final scores and the complaints score. An r of .1 was considered a small, .3 a moderate, and .5 a large relation (Field, 2009). A Benjamini-Hochberg correction was applied, which is considered the best approach in exploratory research (Benjamini & Hochberg, 1995; Thissen, Steinberg, & Kuang, 2002). The false discovery rate was set at .1.

Results

Demographic and clinical characteristics

We included 160 patients with ABI and 91 healthy controls. See Table 4.1 for demographical and clinical characteristics per group. There was a comparable amount of men and women in both groups ($\chi^2(1, n = 252) = 1.76, p = .185$). Healthy controls were higher educated ($\chi^2(2, n = 252) = 6.41, p = .041$) and younger than patients with ABI ($U = 6028.00, z = -2.34, p = .020$)[1]. As expected, patients with ABI scored significantly lower on the MMSE-2 than the healthy controls ($U = 5346.50, z = -3.38, p = .001$). However, only two patients scored below the cut-off of 24, which indicates that our patient sample was only mild cognitively impaired.

[1] We investigated the effect of age and education on performance stability within patients and healthy controls (adjusted p for 18 tests < .003). There is no significant association between age, education and performance stability on our three digital tests, except for one: the older the healthy controls, the lower the stability in time spent within the target on the TMT A (see Appendix 4.2).

Table 4.1. Demographical and clinical characteristics, split for patients and healthy controls

	Patients with ABI (*n* = 161)	***n***	**Healthy controls** (*n* = 91)	***n***
Male (%)	51.6	161	42.9	91
Age in years (mean, SD)	50.81 (14.47)	161	45.68 (17.02)	91
Level of education (%)		161		91
Low	8.7		4.4	
Average	23.6		13.2	
High	67.7		82.4	
MMSE-2 (0–30) (mean, SD)	28.38 (1.71)	158	29.03 (1.33)	90
Below cut-off of 24 (%)	1.2		1.1	
Time ABI onset (median, range)	2y (4m – 32y; 2m)	160		
ABI type (%)		161		
Stroke	49.1			
Traumatic Brain Injury	48.4			
Brain tumour (resection)	2.5			
Lesion side (%)		161		
Left	20.5			
Right	18			
Bilateral	8.7			
Not visible on scan	8.7			
No scan available	44.1			
Complaints scores (0–100) (mean, SD)	27.78 (16.91)	68	3.58 (6.10)	33
Conventional final scores (mean, SD)				
RAVLT immediate recall: Recalled words (0–75)	40.62 (13.10)	158	47.96 (11.33)	91
RAVLT delayed recall: Recalled words (0–15)	8.56 (3.65)	158	10.57 (2.97)	91
TMT A: Completion time (seconds)	43.02 (19.37)	159	32.78 (11.37)	91
TMT B: Completion time (seconds)	89.42 (48.97)	159	64.02 (25.95)	91
Stroop 1: Completion time (seconds)	58.24 (18.91)	151	48.06 (8.80)	89
Stroop 2: Completion time (seconds)	82.90 (18.51)	150	69.64 (11.72)	87
Stroop 3: Completion time (seconds)	138.48 (43.37)	147	113.36 (25.14)	87
Performance stability measures (0–1) (mean, SD)				
RAVLT immediate recall: time between responses	.38 (0.23)	116	.30 (0.20)	72
RAVLT delayed recall: time between responses	.39 (0.34)	147	.27 (0.31)	86
TMT A: drawing speed	.25 (0.28)	69	.31 (0.25)	48
TMT B: drawing speed	.17 (0.23)	69	.24 (0.30)	48
TMT A: time within target	.31 (0.24)	54	.23 (0.24)	44
TMT B: time within target	.26 (0.23)	54	.21 (0.24)	44
Stroop 1: time between responses	.55 (0.30)	142	.29 (0.24)	82
Stroop 2: time between responses	.44 (0.27)	142	.24 (0.22)	82
Stroop 3: time between responses	.39 (0.27)	142	.24 (0.20)	82

Abbreviations: Acquired Brain Injury (ABI); years (y); months (m); Standard Deviation (SD), Mini-Mental State Examination – 2nd version (MMSE-2); Rey Auditory Verbal Learning Test (RAVLT); Trail Making Test (TMT); Stroop Color and Word Test (Stroop). Note. A higher complaints score is indicative for a higher degree of reported complaints. Higher performance stability scores are indicative for a higher number of fluctuations in test performance.

Differences in performance stability between patients with ABI and healthy controls

Rey auditory Verbal Learning Test (RAVLT) – immediate and delayed recall

Regarding the immediate recall, patients with ABI fluctuated more in naming speed (with time between responses as outcome measure) than healthy controls (F (1, 186) = 5.00, p = .027, η^2 = .026). All participants fluctuated more in naming speed in the first trial compared to the following four trials (F (3.68, 744) = 4.97, p = .001, η^2 = .026), and more in the second half of a trial compared to the first half of a trial (F (1, 186) = 132.40, p < .001, η^2 = .416). There were no interaction effects.

Regarding the delayed recall, patients with ABI fluctuated more in naming speed (time between responses) than healthy controls (F (1, 231) = 342.99, p = .003, η^2 = .038). Additionally, all participants fluctuated more in naming speed in the second half of the test compared to the first half (F (1, 231) = 23.83, p < .001, η^2 = .093). There was no interaction effect. See Figure 4.2 for a visualization of the effects.

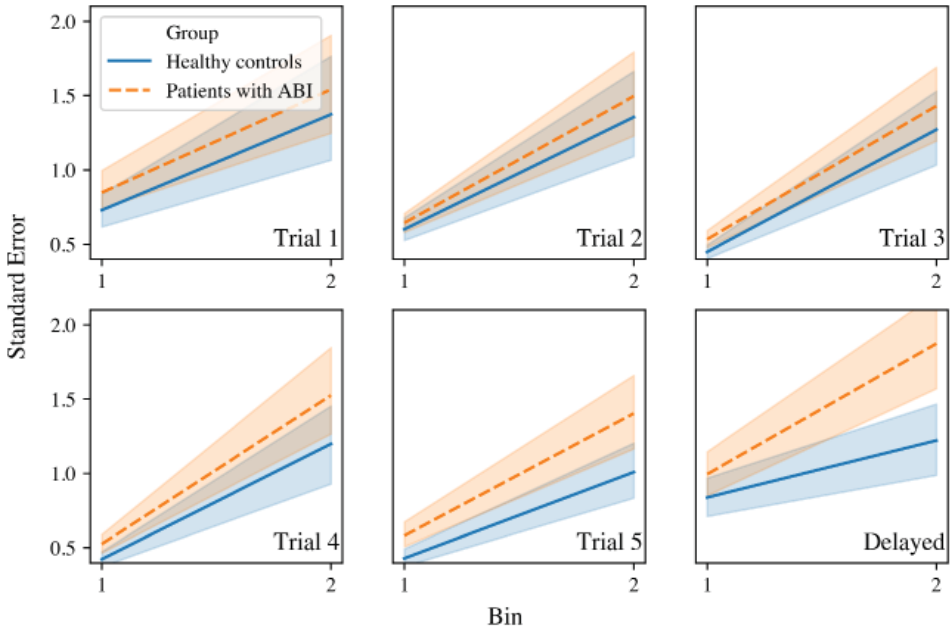

Figure 4.2. Performance stability in naming speed (with time between responses as outcome measure) on the RAVLT immediate recall (trial 1, 2, 3, 4 and 5) and delayed recall at group level. Each trial was divided into 2 bins (horizontal axis). The standard error (as measure of variability) is depicted on the vertical axis. Patients fluctuated significantly more in naming speed compared to healthy controls.

Trail Making Test (TMT) – part A and B

Patients with ABI did not fluctuate more in drawing speed than healthy controls (F (1,115) = 2.47, p = .119, η^2 = .021). All participants fluctuated more in drawing speed in part B compared to part A (F (1, 115) = 22.93, p < .001, η^2 = .166). Additionally, participants fluctuated more in drawing speed in the first bin compared to the second bin, and increasing fluctuations in the last three time bins (F (3.73, 460) = 80.99, p < .001, η^2 = .413). There was an interaction effect of stage and time bin (F (2.97, 460) = 9.15, p < .001, η^2 = .074), indicating that part A reflected a different pattern of fluctuations compared to part B.

Patients with ABI fluctuated more in "thinking/searching time" (with time spent within a target as outcome measures) than healthy controls (F (1, 96) = 4.27, p = .042, η^2 = .043). All participants fluctuated more in "thinking/searching time" in part B compared to part A (F (1, 96) = 144.34, p < .001, η^2 = .601), and more in the first time bin compared to the following four time bins (F (2.76, 384) = 21.50, p < .001, η^2 = .183). There were no interaction effects. See Figures 4.3a and 4.3b for a visualization of the effects.

Stroop Color and Word Test (Stroop) – condition 1, 2 and 3

Patients with ABI fluctuated more in naming speed (with time between responses as outcome measure) than healthy controls (F (1, 222) = 13.83, p < .001, η^2 = .059). All participants showed increasing fluctuations throughout the conditions (F (1.61, 444) = 64.72, p = .001, η^2 = .226). Additionally, all participants fluctuated more in naming speed in the first time bin compared to the following nine time bins (F (3.31, 1998) = 5,02, p < .001, η^2 = .022). There were no interactions effects. See Figure 4.4 for a visualization of the effects.

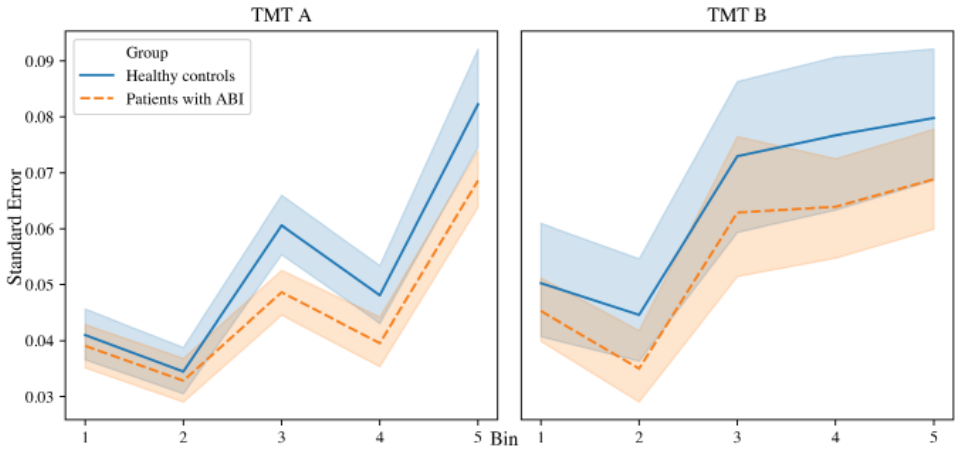

Figure 4.3a. Performance stability in drawing speed on the TMT (part A and B) at group level. Each stage was divided into 5 bins of 5 targets (horizontal axis). The standard error is depicted on the vertical axis. The performance stability in drawing speed of patients and healthy controls was comparable.

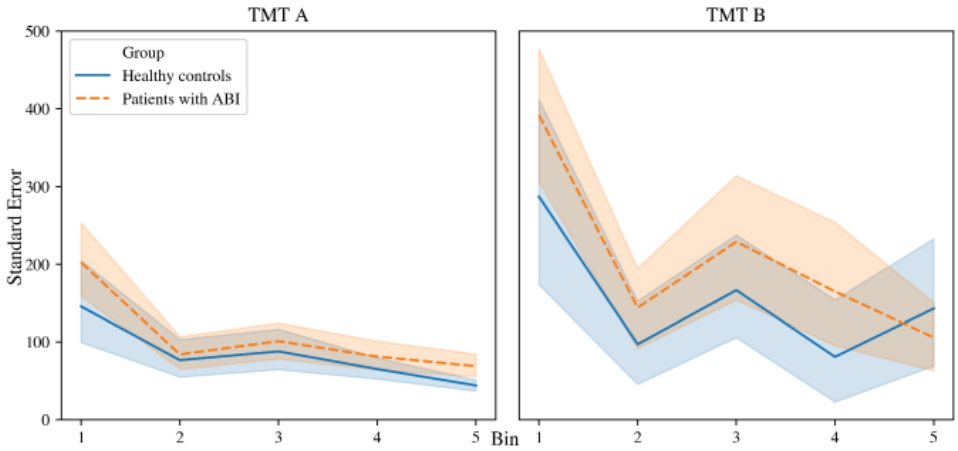

Figure 4.3b. Performance stability in "thinking/searching time" (with time spent within a target as outcome measures) on the TMT (part A and B) at group level. Each stage was divided into 5 bins of 5 targets (horizontal axis). The standard error is depicted on the vertical axis. Patients fluctuated significantly more in "thinking/searching time" compared to healthy controls.

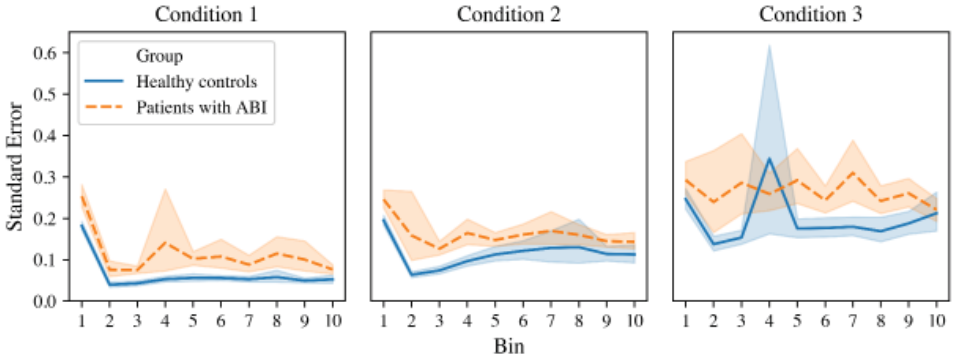

Figure 4.4. Performance stability in naming speed (with time between responses as outcome measure) on the Stroop (condition 1, 2 and 3) at group level. Each condition was divided into 10 bins of 10 words (horizontal axis). The standard error is depicted on the horizontal axis. Patients fluctuated significantly more in naming speed compared to healthy controls.

Added value of performance stability measures in reference to conventional final scores

Overall, 2–12% of patients performed outside normal range on the conventional final scores (defined as < 5th percentile based on data of healthy controls). With regard to the added value, 4–15% of patients performed inside normal range on the conventional final scores, but outside normal range on the performance stability measures (Table 4.2).

Table 4.2. Percentages of patients outside normal range based on performance stability measures in reference to conventional final scores

	Patients performing outside normal range on final scores (%)	***Added value:* patients who performed inside normal range on final scores, but outside normal range on performance stability measures (%)**	***n***
RAVLT Immediate recall: total words x stability	6	10.3	116
RAVLT Delayed recall: total words x stability	10.9	12.2	147
TMT A: total time x stability (drawing speed)	4.3	5.8	69
TMT B: total time x stability (drawing speed)	2.9	4.3	69
TMT A: total time x stability (time within target)	3.7	5.6	54
TMT B: total time x stability (time within target)	1.9	3.7	54
Stroop 1: total time x stability	12	14.8	142
Stroop 2: total time x stability	9.2	4.2	142
Stroop 3: total time x stability	3.5	10.6	142

Relation between final scores, performance stability and cognitive complaints in daily life

There were no significant relations between the conventional final scores and the subjective cognitive complaints, nor between performance stability and the subjective cognitive complaints (Table 4.3).

Discussion

In this study, we capitalized the opportunities afforded by digital neuropsychological tests and developed novel outcome measures targeting performance stability to assess more subtle cognitive impairment. We investigated (1) differences in performance stability between patients with acquired brain injury (ABI) and healthy controls; (2) the added value of performance stability measures for patients with ABI only, in reference to conventional final scores; and (3) the relation between performance stability and cognitive complaints in daily life for patients with ABI.

Patients with ABI fluctuated significantly more in naming speed during the RAVLT and Stroop compared to healthy controls, suggesting that patients responded with a less consistent pace. In the TMT, patients with ABI fluctuated more in "thinking/searching time" compared to healthy controls. On all novel outcome measure patients were clearly dissociable from healthy controls, except for the performance stability in drawing speed during the TMT. This

Table 4.3. Relation between conventional final scores, performance stability measures, and reported cognitive complaints, within patients with ABI only

	Cognitive Complaints Score	
	rs (p-value)	***n***
RAVLT Immediate recall		
Conventional final score (total words)	-.002 (p = .987)	50
Performance stability measure	.15 (p = .286)	50
RAVLT Delayed recall		
Conventional final score (total words)	-.02 (p = .892)	60
Performance stability measure	.24 (p = .069)	60
TMT A Drawing Speed		
Conventional final score (total time)	.19 (p = .301)	31
Performance stability measure	-.31 (p = .094)	31
TMT B Drawing Speed		
Conventional final score (total time)	.41 (p = .022)	31
Performance stability measure	-.44 (p = .013)	31
TMT A Time spent within target		
Conventional final score (total time)	.05 (p = .828)	23
Performance stability measure	-.20 (p = .360)	23
TMT B Time spent within target		
Conventional final score (total time)	.34 (p = .108)	23
Performance stability measure	.04 (p = .848)	23
Stroop Condition 1		
Conventional final score (total time)	.30 (p = .026)	56
Performance stability measure	.16 (p = .241)	56
Stroop Condition 2		
Conventional final score (total time)	.32 (p = .018)	56
Performance stability measure	.29 (p = .029)	56
Stroop Condition 3		
Conventional final score (total time)	.25 (p = .068)	56
Performance stability measure	.17 (p = .216)	56

* No significant p-values based on a Benjamini-Hochberg correction. Note. Higher complaints score are indicative for a higher degree of reported complaints. Higher performance stability scores are indicative for a higher number of fluctuations in test performance.

indicates that healthy controls and patients showed a comparable number of fluctuations in their drawing speed, probably due to accelerations on certain points in the test (e.g., when consecutive targets are not far apart). Furthermore, 2–12% of patients performed outside normal range on the conventional final scores. When developing novel outcome measures, it is important to investigate whether an additional outcome measure improves the diagnostic accuracy by going beyond the available diagnostic information (Moons, De

Groot, Linnet, Reitsma, & Bossuyt, 2012). The added value involves the 4–15% of patients who performed inside normal range on the conventional final scores, but outside normal range on the performance stability measures. This might be considered as an important clinically relevant finding, as we were able to objectify cognitive impairment among those patients, which would not have been objectified with a paper-and-pencil administration. Finally, the performance stability measures, nor the conventional final scores, were associated with cognitive complaints in daily life.

How can we explain the differences in performance stability between patients with ABI and healthy controls? A low stability in test performance might suggest that underlying process, such as fluctuating cognitive effort, affect cognitive function negatively (Milberg et al., 1986). Cognitive effort refers to the extent in which an individual exerts an adequate level of effort to execute a cognitive task. For example, during the TMT, participants fluctuated more in the more complex part of the test (part B), when compared to the less complex part (part A). Performances on part B are associated with more complex visual sequencing and inhibitory control, whereas performances on part A are often associated with primarily visual-scanning and psychomotor processing speed (Fellows, Dahmen, Cook, & Schmitter-Edgecombe, 2017). An elevated number of fluctuations in the more complex stage might reflect an elevated level of cognitive effort that is required from patients to execute the task, suggesting that fluctuations in test performance are more likely to occur during more complex tasks. Another process underlying a low stability in test performance, might involve fluctuations in attention. Because fluctuations in attention are difficult to measure, their effects on behaviour have been difficult to assess. Recent studies have shown that specific cognitive function are not localized to anatomically restricted area, but are rather routed in a widespread brain network linking several cortical areas (Lim & Kang, 2015). By using functional magnetic resonance imaging (fMRI), Rosenberg et al. (2016) demonstrated that the strength of functional brain networks may predict sustained attention in individuals. Although using fMRI during cognitive tasks have been a major focus, the test-retest reliability in individual-differences research have been a concern (Elliott et al., 2020). It seems, therefore, of utmost importance to use cognitive (behavioural) measures to identify fluctuations in attention and their effects on behaviour (i.e., test performance).

The performance stability measures, nor the conventional final scores, were associated with cognitive complaints in daily life. This might be explained by the fact that cognitive impairment (as measured with neuropsychological tests) are not necessarily an indication of cognitive complaints, and vice versa (Clarke, Genat, & Anderson, 2012; Duits, Munnecom, Van Heugten, & Van Oostenbrugge, 2008; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Van Rijsbergen, Mark, De Kort, & Sitskoorn, 2014). Psychological factors

(e.g., coping styles, depressive symptoms) and environmental factors (e.g., domestic or vocational modifications) might influence subjective reports, which is likely the reason why cognitive impairment neither predict or explain cognitive complaints very well (Nijsse et al., 2017). Another explanation might be that neuropsychological tests do not correspond to everyday functioning (Chaytor & Schmitter-Edgecombe, 2003; Spooner & Pachana, 2006). Neuropsychological tests target cognitive functions in isolation (e.g., verbal memory, planning), whereas daily life tasks require multiple cognitive functions at once. In addition, neuropsychological tests are administered under optimal conditions in a quiet and non-distracting environment to elicit the patient's best possible performance. Even though digital tests might open the possibility to develop more sensitive outcome measures (Parsey & Schmitter-Edgecombe, 2013), the setting in which they are administered does still not correspond to daily life. More advanced technologies, such as Virtual Reality, have the potential to assess cognitive impairment in simulated environment resembling daily life (Parsons, McPherson, & Interrante, 2014; Rizzo, Schultheis, Kerns, & Mateer, 2004). However, this study was only a first attempt to develop more sensitive measures to assess more subtle cognitive impairment. More development and research is needed in this area (Parsey & Schmitter-Edgecombe, 2013).

Strengths and limitations

A strength of this study was the inclusion of a large number of patients with ABI (n = 161) and the broad recruitment via clinicians, associations and social media, which increases the representativeness of our sample. Our sample was only mild cognitively impaired (2–12% performed outside normal range on conventional scores), which could be considered as a strength, as developing more sensitive outcome measures is crucial for this group. On the other hand, our findings might not generalize to a more impaired sample. It is, however, to be expected that a low stability in test performance occurs more frequently in patients who are more cognitively impaired, which would have strengthened the results.

We intentionally aimed to include a heterogeneous sample to explore performance stability in patients with ABI. However, one could argue that a heterogeneous sample is a potential limitation, as each brain injury has a different pathology. Injury characteristics were not systematically noted in the medical files, and we were therefore unable to further investigate specific subgroups within our patient sample. For example, it would have been interesting to investigate whether the severity of stroke (e.g., National Institutes of Health Stroke Scale), TBI (e.g., Glasgow Coma Scale, duration loss of consciousness or post-traumatic amnesia) and tumour grade (grade I–V of the World Health Organization) would affect performance stability. Moreover, it might be interesting to investigate the relation of performance stability

and the lesion location or the damage to brain networks, by using brain imaging techniques like diffusion tensor imaging (DTI) on group level. In this study, the time post injury varied between 4 months and 32 years, indicating that patients were in different phases post-injury. Future research should include a large sample of patients, which will allow for the exploration of possible differences in performance stability between specific subgroups regarding clinical characteristics (e.g., diagnosis, severity, time post injury).

Clinical implications

So far, observations of behaviour while performing a test provide important pieces of information regarding performance stability. For instance, neuropsychologists may observe certain behavioural signs that indicate a low stability during a test (i.e., fluctuating between a fast/slow pace, a weakened pace towards the end of the test). Observations, however, might vary significantly among neuropsychologists due to differences in interpretation. Digital tests allow for quantitative measures of performance stability, without interfering with the conventional measures.

Future research

Previous research reported a significant gap in the application of digital tests to further improve cognitive assessment (Parsey & Schmitter-Edgecombe, 2013). This study was just a first step in the development of novel outcome measures assessing performance stability. The "Boston Process Approach" method focusses on the analyses of errors and the process or the means by which a patient reaches a solution to a problem (Kaplan, 1988; Libon, Swenson, Ashendorf, Bauer, & Bowers, 2013; Milberg et al., 1986). Although this process approach is developed to be applied on paper-and-pencil tests, recent research has incorporated the approach in several digital tests (Diaz-Orueta et al., 2020). In our study, we only focussed on performance stability, but additionally integrating the analysis of errors and detection of behavioural patterns might capitalize the opportunities afforded by digital tests.

Furthermore, future research should investigate the underlying processes that might influence performance stability, such as fluctuating attention or cognitive effort. Different psychophysiological techniques including measures of heart function (e.g., heart rate variability), brain activity (e.g., task-evoked brain potentials), and eye-tracking features (e.g., pupillary dilation, blink rate) have been used to measure cognitive effort, cognitive load, (mental) stress or fatigue (Haapalainen, Kim, Forlizzi, & Dey, 2010; Hossain & Elkins, 2018; Paas, Tuovinen, Tabbers, & van Gerven, 2003). For example, the increase or decrease in pupil diameter while processing a cognitive task reflects small differences in cognitive effort. Psychophysiological techniques may provide added value not captured through

behavioural or self-report measures alone, and may provide insight into the underlying processes influencing performance stability.

Conclusions

In this study, we capitalized the opportunities afforded by digital neuropsychological tests and developed novel outcome measures to assess more subtle cognitive impairment. We assessed *performance stability* by evaluating the number of fluctuations in test performance on three digital neuropsychological tests. Patients with ABI showed a higher number of fluctuations in their performance on the RAVLT, TMT and Stroop, when compared to healthy controls. The added value involved the 4–15% of patients who performed inside normal range on the conventional final scores, but outside normal range on the performance stability measures. This study was a first attempt to develop more sensitive measures to assess mild cognitive impairment, which cannot be quantified at this level of (objective) detail with paper-and-pencil tests. More development and research is needed in this area.

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Appendix 4.1. Development of measures of cognitive stability

	Conventional final scores and the cut-off based on the 5th percentiles of healthy controls	**Step 1** Outcome measures	**Step 2** Time bins	**Step 3** Computing 95%CI - Healthy controls	**Step 4** Computing Standard Error (SE) - Individuals	**Step 5** Computing standardized measures	**Data loss**
RAVLT immediate recall (Trial 1–5)	Correct recalled words (0–75); Cut-off: < 26 is considered abnormal (based on healthy controls).	Time between consecutive responses[1]	As the length of a trials differs between participants, we chose 2 bins (total time / 2) per stage = 5 stage x 2 time bins	As measure of variability, the SE and a 95%CI was calculated per time bin based on 72 healthy controls in the immediate condition, and 86 healthy controls in the delayed condition.	The SE was calculated per time bin for each individual patient. The SE could be categorized as below, above or within the 95%CI of healthy controls.	We counted how many times the standard error of a patient fell outside normal range and computed this into a proportion (0–1).	In the immediate stage, we reduced the data loss to 2.8% with linear interpolation, for at most of one consecutive missing timestamp. In the delayed stage, we reduced it to 6.8%. Participants with a missing SE in any time bin (due to > 1 consecutive missing timestamps) were excluded from the analyses, resulting in 72 healthy controls and 116 patients in the immediate condition, and 86 healthy controls and 147 patients in the delayed condition.
RAVLT delayed recall	Correct recalled words (0–15); Cut-off: < 5 is considered abnormal.						
TMT Part A	Completion time part A (seconds); Cut-off: > 61.28 is considered abnormal.	Time spend within target[2], drawing speed[3]	5 bins (5 x 5 targets)	As measure of variability, the SE and a 95%CI was calculated per time bin based on 48 healthy controls with drawing speed as outcome measure, and 44 healthy controls with time spent within target as outcome measure.	The SE was calculated per time bin for each individual patient. The SE could be categorized as below, above or within the 95%CI of healthy controls.	We counted how many times the standard error of a patient fell outside normal range and computed this into a proportion (0–1).	Participants with a missing SE in any time bin (when there were < 2 timestamps) were excluded from the analyses, resulting in 48 healthy controls and 69 patients (with drawing time as outcome measures), and 44 healthy controls and 54 patients (with time spent within target).
TMT Part B	Completion time part B (seconds); Cut-off: > 125.42 is considered abnormal.						

Appendix 4.1 continues on next page.

Appendix 4.1. *Continued*

	Conventional final scores and the cut-off based on the 5th percentiles of healthy controls	**Step 1** Outcome measures	**Step 2** Time bins	**Step 3** Computing 95%CI - Healthy controls	**Step 4** Computing Standard Error (SE) - Individuals	**Step 5** Computing standardized measures	**Data loss**
Stroop Condition 1	Completion time (seconds); Cut-off: > 59.69 is considered abnormal.	Time between consecutive responses[1]	10 bins (10 x 10 items) per stage = 3 stages x 10 time bins	As measure of variability, the SE and a 95%CI was calculated per time bin based on 82 healthy controls.	The SE was calculated per time bin for each individual patient. The SE could be categorized as below, above or within the 95%CI of healthy controls.	We counted how many times the standard error of a patient fell outside normal range and computed this into a proportion (0–1).	A total of 8% of the data was not usable, due to an error in the data files or due to > 1 consecutive missing timestamps. Linear interpolation was not possible due to non-linear data. Participants with a missing SE in any time bin were excluded from the analyses, resulting 82 healthy controls and 142 patients.
Stroop Condition 2	Completion time (seconds); Cut-off: > 93.13 is considered abnormal.						
Stroop Condition 3	Completion time (seconds) Cut-off: > 163.45 is considered abnormal.						

Note. [1] Time between responses was calculated as $interResponseTime = responseTimeStamp_n - startTime$, where n is the first response. For $n > 1$, time between responses was calculated as $interResponseTime = responseTimeStamp_n - responseTimeStamp_{n-1}$. Additionally, the raw datafiles included each response whether it was correct or incorrect; all responses were used regardless of correctness. [2] Time spent within target was calculated as the total amount of time that the participant spent inside a target with the pencil stylus, by subtracting f*irst timestamp crossing the border to enter the target (starting point)*, from *the first timestamp crossing the border to leave the target (endpoint)*. [3] Drawing speed was calculated as the total distance (in pixels) drawing from one target to another target, divided by the time it took a participant to do so.

Appendix 4.2. Effect of age and education on performance stability within patients and healthy controls

	Patients with ABI (n = 161)				**Healthy controls** (n = 91)			
	Age	***n***	**Education**	***n***	**Age**	***n***	**Education**	***n***
Performance stability measures (0–1)								
RAVLT immediate recall: time between responses	rs = .22, p = .021	116	$H(2)$ = 3.46, p = .117	116	rs = .24 (p = .044)	72	$H(2)$ = 2.24, p = .326	72
RAVLT delayed recall: time between responses	rs = .04, p = .625	147	$H(2)$ = 4.23, p = .121	147	rs = .27 (p = .011)	86	$H(2)$ = 0.85, p = .654	86
TMT A: drawing speed	rs = -.18, p = .133	69	$H(2)$ = 4.05, p = .132	69	rs = -.15 (p = .314)	48	$H(2)$ = 1.95, p = .384	48
TMT B: drawing speed	rs = -.01, p = .925	69	$H(2)$ = 1.45, p = .486	69	rs = -.06 (p = .698)	48	$H(2)$ = 1.61, p = .447	48
TMT A: time within target	rs = .31, p = .023	54	$H(2)$ = 8.40, p = .015	54	rs = .55 (p < .001)*	44	$H(2)$ = 2.71, p = .258	44
TMT B: time within target	rs = .27, p = .05	54	$H(2)$ = 6.26, p = .044	54	rs = .34 (p = .023)	44	$H(2)$ = 2.46, p = .293	44
Stroop 1: time between responses	rs = .14, p = .109	142	$H(2)$ = 3.74, p = .154	142	rs = .20 (p = .067)	82	$H(2)$ = 3.58, p = .167	82
Stroop 2: time between responses	rs = .18, p = .029	142	$H(2)$ = 2.39, p = .303	142	rs = .21 (p = .063)	82	$H(2)$ = 5.53, p = .063	82
Stroop 3: time between responses	rs = .11, p = .18	142	$H(2)$ = 1.53, p = .465	142	rs = .22 (p = .052)	82	$H(2)$ = 2.69, p = .261	82

* Adjusted p for 18 tests < .003.

Part III

Advanced technology

On November 17th in 2013, I went upstairs to visit the bathroom, when I fell to the ground. I got off the floor and I carefully went down the stairway. I remember thinking that our stairway was really steep and scary. My wife noticed one side of my mouth had dropped and that I was talking funny. She asked a neighbor to check on me and he called an ambulance. I did not feel or notice anything myself. The doctors told me I suffered from a major stroke. Only after a few days, I noticed several changes. The left side of my body was numb and I had difficulty concentrating. One time, I did not recognized my arm as my own arm. After being hospitalized for a week, I was referred to a rehabilitation center where I stayed for four months. I felt really unhappy. I couldn't do anything by myself and was completely dependent of others. Honestly, I did not feel like a human being anymore. As part of the therapy, I was trained to do things without the help of others. They found out that I suffer from the neglect syndrome. With my wheelchair I bumped into the left side of doorposts. I tried to think about my left side, but I bumped into things anyway. It has improved, but it still affects me every day. When I enter an elevator I sometimes hit my left shoulder on the left side of the opening. When researchers think of something to make it better for people with neglect, I participate in the research. Nowadays, I am doing pretty well, but I am still in a wheelchair. It feels like a daily confrontation of what happened to me. I still have to deal with the consequences of the stroke every day. On the other side, I am also happy with my wheelchair, it gives me the possibility to get out of the house.

Chapter 5

Increasing cognitive demand in assessments of visuo-spatial neglect: Testing the concepts of static and dynamic tests

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Abstract

Introduction: Numerous tests of visuo-spatial neglect (VSN) have been developed. In this study, we propose a clustering of VSN tests by making a distinction between static tests with low levels of cognitive demand (i.e., tests without movement or time-restrictions, such as paper-and-pencil tests) and dynamic tests with high levels of cognitive demand (i.e., tests incorporating movement and time-restrictions, such as virtual reality tests). The concepts of static and dynamic tests have not been systematically investigated so far. Here, we investigated (1) whether we would find dissociations between patients showing VSN on test within the static cluster but not on tests within the dynamic cluster, and vice versa; (2) whether differences in demographic or clinical characteristics could be identified between these groups of patients; and (3) whether the underlying factor structure would correspond to our proposed distinction between static and dynamic clusters of tests.

Method: Sixty-one patients with VSN completed three static tests (shape cancellation, line bisection, letter cancellation) and three dynamic tests (Catherine Bergego Scale, Mobility Assessment Course, simulated driving test).

Results: 13% of patients showed VSN on tests within the static cluster, 33% on tests within the dynamic cluster, and 54% on tests within both clusters. Patients with VSN on the dynamic tests (alone or in addition to static tests) had poorer motor function, poorer walking abilities and were more dependent in daily life than patients showing VSN on the static cluster alone. The underlying factor structure corresponded to our proposed conceptual distinction between static and dynamic clusters of tests.

Conclusions: Static and dynamic tests compose different clusters and double dissociations are shown between clusters. Future research involving data-driven approaches might result in a better understanding on how different tests of VSN relate to each other, and, more importantly, a better understanding of VSN and its phenotypes.

Introduction

Patients with visuo-spatial neglect (VSN) fail to attend stimuli presented at the contralesional side of space (Buxbaum et al., 2004; Heilman, Valenstein, & Watson, 2000). These patients manifest symptoms such as bumping into doorframes, eating food from only one side of their plate, and ignoring people who are located at their contralesional side (Corbetta, 2014). VSN is known to negatively affect rehabilitation outcomes, such as functional recovery (Nijboer, van de Port, Schepers, Post, & Visser-Meily, 2013), motor recovery (Nijboer, Kollen, & Kwakkel, 2014), and reintegration into the community (Chen, Hreha, Kong, & Barrett, 2015). In general, patients with VSN require more help and ongoing assistance from caregivers, which increases caregivers' burden and stress levels (Bosma, Nijboer, Caljouw, & Achterberg, 2020; Chen, Fyffe, & Hreha, 2017). Given its negative effect, early detection of VSN is crucial to start appropriate treatment.

A clinical assessment is needed to objectify the presence and severity of VSN (Azouvi et al., 2006). VSN is usually assessed with neuropsychological paper-and-pencil tests, such as cancellation, line bisection, and copying tests. Previous research has reported a lack of ecological validity, since the level of cognitive demand in paper-and-pencil tests does not resemble the high level of cognitive demand of daily life (Azouvi, 2017; Tsirlin, Dupierrix, Chokron, Coquillart, & Ohlmann, 2009). Cognitive demand refers to the level of cognitive resources that are required to execute a task, which varies as a function of task complexity (Tsaparli, 2014). Task complexity can be directly related to task features that increase information load, information diversity, or rate of information change (Campbell, 1988; Liu & Li, 2012). For more complex tasks, patients are required to invest more cognitive resources during task performance. In paper-and-pencil tests, there are no changing stimuli, external distractions, or time-restrictions, which emphasizes the "static" nature and the low level of cognitive demand in these tests (Pedroli, Serino, Cipresso, Pallavicini, & Riva, 2015; Ten Brink, Visser-Meily, & Nijboer, 2018).

To improve ecological validity, dynamic tests have been developed to relate to the level of cognitive demand of daily life (Blini et al., 2016; Bonato, 2012; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010). In this study, we consider tests to be "dynamic" when stimuli change as a patient moves through an environment, when performance is time-bound, and/or when a patient is required to multitask (Bonato, 2012; Spreij, Ten Brink, Visser-Meily, & Nijboer, 2020; Ten Brink et al., 2018). When patients are moving, there is more attentional competition between stimuli at the ipsilesional versus the contralesional side of space than in a motionless situation (Bonato, 2012). There is little time to attend to objects as stimuli are on the retina for a short amount of time, and there is strong competition between objects

that draw attention. Patients with VSN will, consequently, have more difficulties disengaging attention from the ipsilesional side to attend the contralesional side (Rengachary, d'Avossa, Sapir, Shulman, & Corbetta, 2009; Ten Brink et al., 2018). Observational scales, such as the Catherine Bergego Scale (CBS), can be considered dynamic, as they provide a systematic evaluation of VSN behaviour during activities of daily living (ADL) in a real-life setting (Azouvi et al., 2003; Ten Brink et al., 2013). An example of an objective quantified test is the Mobility Assessment Couse (MAC), where participants navigate through a hallway while searching for targets (Grech, Stuart, Williams, Chen, & Loetscher, 2017; Ten Brink et al., 2018; Verlander et al., 2000). An additional advantage of the MAC is that patients are required to perform several operations at once (navigating and searching), which makes a test like the MAC even more demanding than for example a cancellation test, where searching for targets is the only required operation (Blini et al., 2016; Bonato et al., 2010). Multitasking may lead to competition for cognitive resources (Künstler et al., 2018; Rengachary et al., 2009; Schaefer, 2014; Ten Brink et al., 2018), and performance will suffer when attentional abilities are weakened (Bonato, 2012, 2015; Bonato et al., 2010). Finally, Virtual Reality has been used to assess VSN in a controlled environment that simulates daily life situations (Pallavicini et al., 2015; Tsirlin et al., 2009). For example, we have used a simulated driving test to assess VSN (Spreij et al., 2020).

Numerous tests of VSN have been developed, varying in level of cognitive demand. In this study, we propose making a distinction between static tests, with low levels of cognitive demand, and dynamic tests, with high levels of cognitive demand. It is not simply the case that dynamic tests are more challenging than static tests, as extensive research has showed dissociations between performances on static versus dynamic tests (Azouvi, 2002; Azouvi et al., 2006; Grattan & Woodbury, 2017; Hamilton, Coslett, Buxbaum, Whyte, & Ferraro, 2008). For example, patients may show VSN on the MAC or a Virtual Reality test, but not on a cancellation test, and vice versa (Azouvi et al., 2006; Grech et al., 2017; Peskine et al., 2011; Spreij et al., 2020; Ten Brink et al., 2018). These dissociations suggest a conceptual distinction between static and dynamic tests – two concepts that are often used by clinicians and researchers to describe VSN assessments (e.g., Deouell, Sacher, & Soroker, 2005; Smit et al., 2013; Spreij et al., 2020; Ten Brink et al., 2017; Toglia & Cermak, 2009). However, these concepts have not been systematically investigated in a large cohort of VSN patients with multiple tests. To gain a better understanding in this matter, we propose a clustering of VSN tests by making a distinction between static tests and dynamic tests. We hypothesized to find dissociations between patients showing VSN on tests within the static cluster but not on tests within the dynamic cluster, and vice versa. We evaluated whether differences in demographic or clinical characteristics could be identified between these groups of

patients. Finally, we hypothesized that in case tests from the same cluster were part of the same concept (static versus dynamic), the underlying factor structure would correspond to our proposed distinction between static and dynamic clusters of tests.

Materials and methods

Participants

A total of 70 stroke patients were included in a randomized control trial, investigating prism adaptation in rehabilitation (#NTR3278; approved by the Medical Ethical Committee of the University Medical Center Utrecht and De Hoogstraat Rehabilitation Center, #12-183/O) (Ten Brink, Visser-Meily, & Nijboer, 2015). Inclusion criteria for the randomized controlled trial were: (1) clinically diagnosed stroke (confirmed by an MRI or CT scan); (2) indication of VSN based on the performance on the shape cancellation, line bisection and/or CBS; (3) age between 18 and 85 years old; and (4) sufficient comprehension and communication (evaluated by a neuropsychologist). Exclusion criteria were: (1) interfering psychiatric disorders and/or substance abuse; (2) expected discharge < 4 weeks; and (3) physically or mentally unable to participate (evaluated by a rehabilitation physician). Written informed consent was obtained from all patients. The experiment was performed in accordance with the Declaration of Helsinki.

In order to compute *z*-scores of the patients' test performances, we recruited healthy controls (for the shape cancellation, line bisection, letter cancellation, MAC and simulated driving test) and stroke patients without VSN (for the CBS) as control groups. We used stroke patients without VSN as control group for the CBS, since the comparison between patients with and without VSN provides information on the role of VSN on ADL. The inclusion criteria for the healthy controls were (1) aged between 18–80 years old; and (2) no history of neurological and/or psychiatric disorders. The inclusion criteria for the stroke patients without VSN were: (1) clinical diagnosed stroke (confirmed by an MRI or CT scan); (2) aged between 18 and 80 years old; and (3) no indication of VSN based on the shape cancellation and/or CBS.

Tests and outcome measures

The baseline measurement of the randomized control trial consisted of three static tests (shape cancellation, line bisection, letter cancellation) and three dynamic tests (CBS, MAC, simulated driving test). The test session lasted ± 60 minutes in total.

Static VSN tests

The static tests (shape cancellation, line bisection, letter cancellation) were administered using a 22-inch interactive WACOM (PL2200) tablet screen (1920 × 1080), with a screen size of 477.64 mm × 268.11 mm (Smit et al., 2013). The tablet screen was oriented horizontally and slightly tilted with an angle of 18 degrees. Participants were seated in front of the tablet screen at a distance of approximately 30 cm. They had to respond to the stimuli by drawing on the screen with a digital stylus. DiagnoseIS (developed by Metrisquare, the Netherlands) was used to program the static tests.

Shape cancellation

The digitized shape cancellation consisted of 56 targets (small shapes) and 75 distractors in different sizes (shapes, letters, and words). Two targets in the centre were marked by the researcher as part of the instruction. Patients were instructed to designate the remaining 54 targets (27 left, 27 right) and tell the examiner when they had completed the test. No time limit was given. The asymmetry score was calculated (number of missed targets on the right – number of missed targets on the left). As left-sided VSN would result in a negative value and right-sided VSN in a positive value, the absolute value was used in order to be able to compare patients with left- and right-sided VSN. The range of the absolute asymmetry score was between 0 (equal number of missed targets on the left and right side) and 27 (27 missed targets on one side and 0 missed targets on the other side). We used the average asymmetry score (0.32) and standard deviation (0.57) of 22 healthy controls to compute *z*-scores.

Line bisection

The digitized line bisection test was based on the Behavioural Inattention Test (Wilson, Cockburn, & Halligan, 1987), where each patient was presented with three horizontal lines (320 mm each; 1 mm thick) that were displayed in a staircase fashion. This subtest of the BIT was administered twice. Patients were instructed to mark the midpoint of each line. We measured the deviations from the true midpoint (deviations to left scored as negative; deviations to the right as positive). Next, the average deviation of the six lines was calculated and computed to an absolute score. The maximum deviation was 160 mm (320 mm deviated by 2). We used the average deviation (4.82 mm) and standard deviation (4.05 mm) of 22 healthy controls to compute *z*-scores.

Letter cancellation

The digitized letter cancellation consisted of 5 rows of 34 letters (170 letters in total) (Smit et al., 2013). Participants were instructed to cancel the target letters "E" and "R" (20 left, 20 right), which were randomly placed between the distractor letters. The asymmetry score was

calculated (number of missed targets on the right – number of missed targets on the left). As left-sided VSN would result in a negative value and right-sided VSN in a positive value, the absolute value was used. The range of the absolute asymmetry score was between 0 (equal number of missed targets on the left and right side) and 20 (20 missed targets on one side and 0 missed targets on the other side). We used the average asymmetry score (0.36) and standard deviation (0.66) of 22 healthy controls to compute *z*-scores.

Dynamic VSN tests

Catherine Bergego Scale

The CBS is an observation scale to assess VSN behaviour during ADL (Azouvi, 2002). The nursing staff observed and rated behaviour during 10 activities (e.g., dressing or eating), providing a score of 0 (no VSN) to 3 (severe VSN) per item. Items that were missing (e.g., due to the inability to independently perform an activity or when a situation was not observed) were considered invalid. The total score was the sum of the valid item scores, divided by the number of valid items, multiplied by 10 (resulting in a total score ranging from 0 [no VSN] to 30 [severe VSN]). To compute *z*-scores, we used the average score (1.03) and standard deviation (2.08) of 58 stroke patients without VSN.

Mobility Assessment Course

The MAC is a visual search test that is conducted in a corridor (Ten Brink et al., 2018). Participants were instructed to follow 5 directional indicators and find 24 targets (yellow squares, 10 cm × 10 cm) attached to the wall (12 left, 12 right). We corrected for targets that were invisible (i.e., targets obstructed by an object or person), by dividing the number of omissions by the number of visible targets, and multiply this by the total number of targets. The asymmetry score was calculated (number of missed targets on the right – number of missed targets on the left). As left-sided VSN would result in a negative value and right-sided VSN in a positive value, the absolute value was used. The range of the absolute asymmetry score was between 0 (equal number of missed targets on the left and right side) and 12 (12 missed targets on one side and 0 missed targets on the other side). We used the average asymmetry score (0.89) and standard deviation (0.80) of 31 healthy controls to compute *z*-scores.

Simulated driving test

The simulated driving test (Spreij et al., 2020) consisted of a straight road without intersections or oncoming traffic projected on a large screen (2.13 m × 3.18 m). A steering wheel was fixed on a table at a distance of 90cm from the projection screen. Participants

were instructed to maintain their starting position (the centre of the right lane) by using the steering wheel. Participants needed to adjust their position as they were 'blown' of track due to 'side wind' manipulations from both directions. The total test took 2 minutes. Outcome measures consisted of the average position on the road for every 15 seconds (resulting in 8 values in total). The total range of position was between -600 (the left verge) and up to 200 (the right verge), with 0 indicating the centre of the right lane. We computed the absolute average deviation from 0, based on the 8 values. We used the average deviation (27.03) and standard deviation (26.70) of 36 healthy controls to compute *z*-scores.

Demographic and clinical characteristics

We collected data on sex, age, and level of education from the medical files. Level of education was assessed by using a Dutch classification system (Verhage, 1965) that consists of 7 levels, with 1 being the lowest (less than primary school) and 7 being the highest (academic degree). These levels were converted into three categories for analysis: low (Verhage 1–4), average (Verhage 5), and high (Verhage 6–7). This Dutch classification system is the most commonly used system in the Netherlands and is similar to the International Standard Classification of Education (UNESCO Institute for Statistics, 2011).

We extracted stroke type (ischaemic, haemorrhage, or cerebral ischemia after subarachnoid haemorrhage), lesion side (left, right, both), and number of days post-stroke onset from the medical files. VSN has been associated with slower and poorer recovery patterns of motor impairment (Katz, Hartman-Maeir, Ring, & Soroker, 1999; Nijboer, Kollen, et al., 2014), as well as limitations in ADL (Bosma et al., 2020; Katz et al., 1999; Nijboer et al., 2013), postural imbalance (Nijboer, Ten Brink, Van der Stoep, & Visser-Meily, 2014; Van Nes et al., 2009), and walking disabilities (Nijboer et al., 2013). We extracted the scores on several clinical variables that were administered at admission to test the association between motor impairment and VSN. Independence during ADL was measured with the Barthel Index (Collin, Wade, Davies, & Horne, 1988). Motor strength of upper and lower extremities was measured with the Motricity Index (Collin & Wade, 1990). Independence during walking was measured with the Functional Ambulation Classification (Holden, Gill, Magliozzi, Nathan, & Piehl-baker, 1984). Communication skills were measured with the Stichting Afasie Nederland test (Deelman, Koning-Haanstra, Liebrand, & Van den Burg, 1981).

We extracted scores on cognitive tests from the medical files, which were administered as part of a neuropsychological assessment as care as usual. Global cognitive functioning was measured with the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) or the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). In order

to create one score for global cognitive functioning, the MMSE score was converted into a MoCA score by using the following formula: MoCA = (1.124 × MMSE) – 8.165 (Solomon et al., 2014). In addition, memory function was measured with the Rey Auditory Verbal Learning Test (Rey, 1941), and executive functions were measured with the Tower Test (Delis, Kaplan, & Kramer, 2007).

Statistical analyses

Categorizing patients based on their performances on VSN tests

We translated the raw scores of each test into standardized *z*-scores using the following formula:

$$\frac{score - average\ score}{standard\ deviation}$$

The average score and standard deviation were based on the performance of healthy controls (shape cancellation, line bisection, letter cancellation, MAC and simulated driving test) or stroke patients without VSN (CBS). We averaged the *z*-scores of the static tests (shape cancellation, line bisection, letter cancellation) and the *z*-scores of the dynamic tests (CBS, MAC, simulated driving) to compute scores per cluster. We considered an average *z*-score of above 2 to be indicative for VSN. An average *z*-score of multiple tests provides the most reliable indication of a deficit, as each test is taken equally into account (Evans, 1996). Based on the average *z*-scores, patients were categorized as: (1) patients showing VSN on tests within the static cluster and not within the dynamic cluster; (2) patients showing VSN on tests within the dynamic cluster and not within the static cluster; and (3) patients showing VSN on tests within both the static and dynamic cluster. We provided the percentage of patients per group. Patients were excluded when (1) data was missing on more than one static or dynamic test; and (2) they did not show VSN in both clusters (defined as an average *z*-score below 2 on tests within the static and dynamic cluster) during the baseline measurement (approximately two weeks after the VSN screening).

Comparison of demographic and clinical characteristics between the groups

We compared demographic and clinical characteristics between the three groups using non-parametric tests (Kruskal-Wallis non-parametric ANOVA and post-hoc Mann-Whitney *U* tests for continuous variables, and Chi-square test for categorical variables). Effect sizes were calculated for the Mann-Whitney *U* tests by using Pearson's correlation coefficient (*r*). While the Bonferroni correction is the best-known method to counteract the problem for multiple comparisons, this correction results quickly in disregarding significant observations

(Rothman, 1990; Simes, 1986). Therefore, a Benjamini-Hochberg correction was applied, which is considered the best approach in exploratory research (Benjamini & Hochberg, 1995; Thissen, Steinberg, & Kuang, 2002). The false discovery rate was set at .1 (Appendix 5.1ab).

Factor structure underlying performances on VSN tests: static and dynamic clusters

A Confirmatory Factor Analysis (CFA) was performed, using the lavaan R package (Rosseel, 2012), to confirm whether the underlying factor structure would correspond to our proposed distinction between static and dynamic clusters of tests. CFA explicitly tests *a priori* hypotheses about relations between observed variables (e.g., test scores) and an underlying factor structure (Jackson, Gillaspy, & Purc-Stephenson, 2009). We hypothesized that in case tests from the same cluster were part of the same concept (static versus dynamic), the data would be more consistent with a two-factor model than with a one-factor model. In a one-factor model, we assumed that there was one general factor underlying all test scores. In a two-factor model, we hypothesized that there were two factors underlying the test scores, namely the *shape cancellation asymmetry score (absolute)*, *line bisection averaged deviation score (absolute)* and the *letter cancellation asymmetry score (absolute)* loading on the static cluster factor, and the *CBS total score*, *MAC asymmetry score (absolute)*, and the *average position on the road during simulated driving (absolute)* loading on the dynamic cluster factor.

After estimating the two models, we performed a likelihood ratio test to compare how consistent each of these models are with the observed data. We also computed a Chi-square goodness-of-fit test (χ^2) to test the consistency of the data with the proposed models. Four further fit indices were used to evaluate the models: Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR), Comparative Fit Index (CFI), and the Tucker-Lewis index (TLI). A RMSEA and SRMR of ≤ .08 are usually considered adequate fit, and a CFI and TLI of ≥ .95 are considered good fit (Hooper et al., 2008). We used Full Information Maximum Likelihood (FIML) for missing data, which estimates the missing values based on the data.

Results

For the current study, 9 patients were excluded based on the following criteria: (1) no data on more than one static test or more than one dynamic test (n = 1); (2) the average z-score on tests within the static and dynamic cluster was below 2, which was indicative for no VSN (n = 8). In total, 61 patients were included.

Categorizing patients based on their performances on VSN tests

Based on the performances on tests within the static cluster and dynamic cluster, we found that 13% of patients (n = 8) showed VSN on tests within the static cluster alone, 33% of patients (n = 20) showed VSN on tests within the dynamic cluster alone, and 54% of the patients (n = 33) showed VSN on tests within both the static and dynamic cluster. The z-scores for each individual test are presented per group in Figure 5.1. The average z-scores per cluster are presented in Table 5.1.

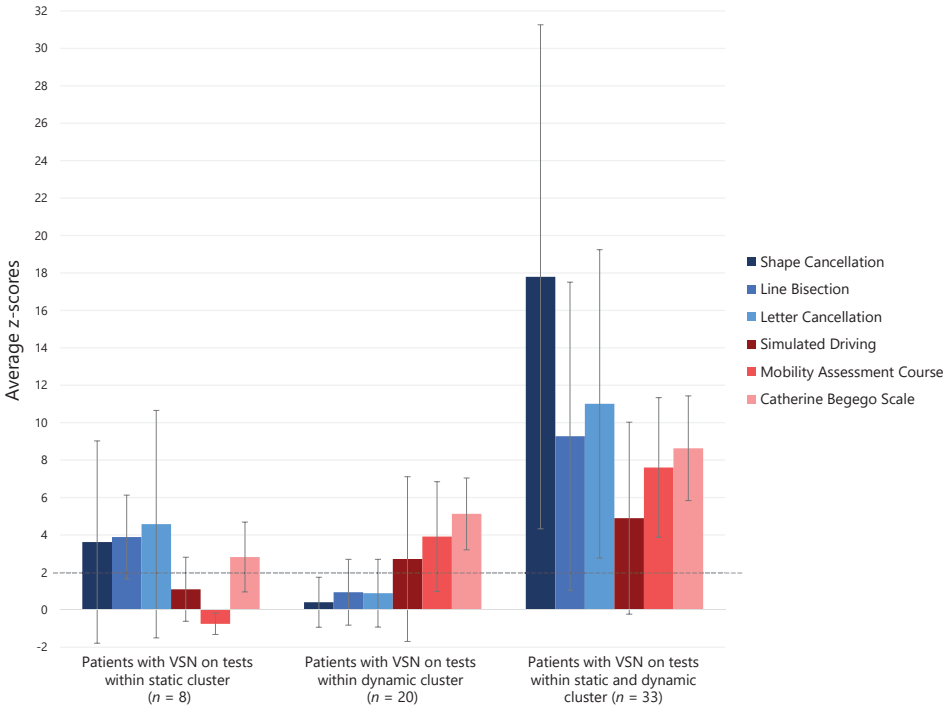

Figure 5.1. On the x-axis the three groups are depicted: (1) patients with visuo-spatial neglect (VSN) on tests within the static cluster alone; (2) patients with VSN on tests within the dynamic cluster alone; and (3) patients with VSN on tests from both the static and dynamic cluster. On the y-axis the average z-scores on each individual VSN test (shape cancellation, line bisection, letter cancellation, CBS, MAC, simulated driving test) is depicted. An average z-score above two (indicated by the dotted line) was used as an indication for VSN. The error bars represent the variability (SD).

Comparison of demographic and clinical characteristics between the groups

There were no significant differences in sex, age, level of education, stroke type, lesion side, number of days post-stroke onset, global cognitive functioning, memory function or executive functions between the three groups (Table 5.1). We found significant differences in motor strength in upper and lower extremities, independence during ADL, and independence during walking between the three groups. Patients who showed VSN on tests

Table 5.1. Demographic and clinical characteristics split per group

	Patients with VSN on tests within static cluster (*n* = 8)	***n***	**Patients with VSN on tests within dynamic cluster** (*n* = 20)	***n***	**Patients with VSN on tests within static and dynamic cluster** (*n* = 33)	***n***	**Statistics**
Sex (% male)	62.5	8	90	20	63.6	33	$\chi^2(2, N = 61) = 4.73, p = .094$
Age in years (mean, SD)	62.41 (6.30)	8	59.68 (12.10)	20	59.34 (8.58)	33	$H(2) = 0.63, p = .731$
Level of education (%)		8		19		32	$\chi^2(4, N = 59) = 0.50, p = .974$
Low	37.5		26.3		28.1		
Moderate	37.5		36.8		37.5		
High	25		36.8		34.4		
Stroke type (%)		5		18		28	Fisher's = 2.37, $p = .684$
Ischemic	60		72.2		71.4		
Haemorrhage	40		27.8		21.4		
Subarchnoid haemorrhage	0		0		7.1		
Lesion side (%)		7		20		33	Fisher's = 7.20, $p = .078$
Left	28.6		30		6.1		
Right	71.4		65		90.9		
Both	0		5		3		
Days post stroke (mean, SD)	33.13 (15.81)	8	54.55 (29.59)	20	53.61 (29.98)	33	$H(2) = 5.09, p = .078$

Table 5.1. *Continued*

	Patients with VSN on tests within static cluster (*n* = 8)	***n***	**Patients with VSN on tests within dynamic cluster** (*n* = 20)	***n***	**Patients with VSN on tests within static and dynamic cluster** (*n* = 33)	***n***	**Statistics**
Stichting Afasie Nederland test, 1–7 (mean, SD)	5.25 (1.99)	6	5.25 (1.81)	16	6.00 (1.43)	30	$H(2) = 2.98, p = .225$
Barthel Index, 0–20 (mean, SD)	13.25 (4.17)	6	6.82 (4.05)	19	7.25 (4.48)	28	$H(2) = 8.09, p = .018$*
Motricity Index upper, 0–100 (mean, SD)	87.00 (26.83)	5	23.86 (38.74)	14	30.48 (36.84)	27	$H(2) = 10.45, p = .005$*
Motricity Index lower, 0–100 (mean, SD)	91.40 (10.99)	5	32.69 (41.59)	16	45.52 (36.09)	27	$H(2) = 9.09, p = .011$*
Functional Ambulation Categories, 0–5 (mean, SD)	3.69 (1.28)	8	2.65 (1.09)	20	2.22 (1.47)	32	$H(2) = 7.42, p = .025$*
Montreal Cognitive Assessment, 0–30 (mean, SD)	15.32 (7.77)	7	20.55 (4.11)	17	18.87 (4.48)	26	$H(2) = 2.82, p = .244$
RAVLT Immediate recall 0–75 (mean, SD)	27.40 (9.71)	5	34.06 (11.96)	16	34.30 (8.86)	27	$H(2) = 2.21, p = .331$
RAVLT Delayed recall 0–15 (mean, SD)	5.20 (2.95)	5	6.20 (4.51)	15	6.41 (3.33)	27	$H(2) = 0.81, p = .666$
RAVLT Recognition 0–30 (mean,SD)	24.60 (3.36)	5	26.80 (3.95)	15	26.22 (3.61)	27	$H(2) = .2.27, p = .322$
D-KEFS Tower test 0–30 (mean, SD)	12.50 (2.07)	6	12.27 (5.06)	11	11.06 (4.39)	17	$H(2) = 0.97, p = .616$
Z-score on static tests (mean, SD)	4.03 (1.85)	8	0.78 (.81)	20	12.69 (7.98)	33	
Z-score on dynamic tests (mean, SD)	1.06 (.63)	8	3.97 (1.84)	20	7.13 (2.90)	33	

* Significant *p*-value based on a Benjamini-Hochberg correction (Appendix 5.1a). Note that group sizes differ per variable based on the clinical data that was available.
Abbreviations: standard deviation (SD); Rey Auditory Verbal Learning Test (RAVLT); Delis–Kaplan Executive Function System (D-KEFS).

within the dynamic cluster had less strength in both the upper (Appendix 5.1b; U = 8.00, z = -2.69, p = .007, r = -.49) and lower extremities (U = 11.50, z = -2.45, p = .014, r = -.45) compared to patients who showed VSN on tests within the static cluster only. Patients who showed VSN on tests within both the static and dynamic cluster had also less strength in the upper (U = 10.00, z = -3.12, p = .002, r = -.49) and lower extremities (U = 12.00, z = -2.94, p = .003, r = -.46) compared to patients who showed VSN on tests within the static cluster only, but not compared to patients who showed VSN on tests within the dynamic cluster only. Furthermore, patients who showed VSN on tests within the dynamic cluster were more dependent in ADL (U = 15.00, z = -2.68, p = .007, r = -.49) compared to patients who showed VSN on tests within the static cluster. Patients who showed VSN on tests within both the static and dynamic cluster were also more dependent in ADL (U = 25.00, z = -2.68, p = .007, r = -.42) than patients who showed VSN on the static cluster only, but not compared to patients who showed VSN on tests within the dynamic cluster only. Finally, patients who showed VSN on tests within the dynamic cluster were more dependent during walking (U = 39.00, z = -2.12, p = .034, r = -.39) than patients who showed VSN on tests within the static cluster. Patients who showed VSN on tests within both the static and dynamic cluster were more dependent during walking (U = 57.50, z = -2.42, p = .015, r = -.38) compared to patients who showed VSN on tests within the static cluster only, but not compared to patients who showed VSN on tests within the dynamic cluster only.

To summarize, patients who showed VSN on tests within the dynamic cluster (alone or in combination with the static cluster) had poorer motor function (upper and lower extremities), were more dependent in ADL, and more dependent during walking compared to patients who showed VSN on the static cluster only.

Factor structure underlying performances on VSN tests: static and dynamic clusters

Results of the CFA showed that the two-factor model (static versus dynamic) was significantly more consistent with the data than the general factor model ($\chi^2(1) = 7.06$, p = .008), which indicates that the underlying factor structure corresponds well to our proposed conceptual distinction between a static cluster of tests (shape cancellation, line bisection, letter cancellation) and a dynamic cluster of tests (CBS, MAC, simulated driving). All fit indices indicated excellent fit for the static-dynamic factor model: RMSEA .025 and SRMR .043 (smaller than .08), and CFI .997 and TLI .994 (larger than 0.95). The reliability of the static-dynamic factor model was considered high, since there were strong factor loadings (> .7) and the explained variances were > .3 for all tests. There was a moderate relation between the static and dynamic factors (estimated at .46, 95%CI [0.29, 0.63]), which is expected since all tests measured VSN. See Figure 5.2 for a graphical representation of the static-dynamic factor model.

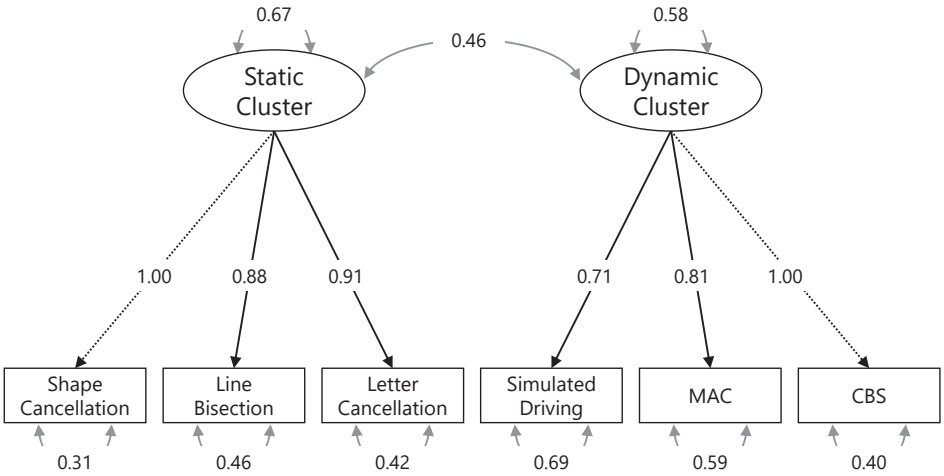

Figure 5.2. A graphical representation of the static-dynamic factor model, supporting our proposed distinction between static and dynamic cluster of tests.

Discussion

In this study, we propose a clustering of VSN tests by making a distinction between static tests with low levels of cognitive demand and dynamic tests with high levels of cognitive demand. We investigated (1) whether we would find dissociations between patients showing VSN on test within the static cluster but not on tests within the dynamic cluster, and vice versa; (2) whether differences in demographic or clinical characteristics could be identified between these groups of patients; and (3) whether the underlying factor structure would correspond to our proposed distinction between static and dynamic clusters of tests.

Indeed, there were dissociations between patients who showed VSN on tests within the static cluster but not on tests within the dynamic cluster, and vice versa. The majority of the patients, namely 54%, showed VSN on tests within both clusters, 33% only on tests within the dynamic cluster, and 13% only on tests within the static cluster. In addition, confirmatory factor analyses showed that the underlying factor structure corresponds to our proposed conceptual distinction between static and dynamic clusters of tests. Our results indicated coherence among tests within the same cluster (static and dynamic), which might suggest that these manifestations represent different phenotypes of VSN. How can we explain these dissociations? Patients showing VSN on dynamic tests while performing well on static tests seems intuitive, because of the underlying assumption that attentional resources are limited. In the dynamic tests, changing surroundings and/or multitasking may lead to competition for cognitive resources (Künstler et al., 2018; Rengachary et al.,

2009; Schaefer, 2014; Ten Brink et al., 2018), and performance will suffer when attentional abilities are weakened (Bonato, 2012, 2015; Bonato et al., 2010). The subset of patients who showed VSN on static tests only might be harder to explain. Possibly, these patients benefit from the dynamic nature of more ecological-valid tests, due to motivation or multisensory stimulation (Tinga et al., 2016). Another explanation might be a phenomenon known as *stochastic resonance* (Moss, Ward, & Sannita, 2004; Söderlund & Sikström, 2008). Hence, where some patients are disturbed by noise (external distractors) during cognitive tasks, others benefit from noise as it increases the level of arousal or general responsivity (Manly, Hawkins, Evans, Woldt, & Robertson, 2002; Söderlund, Sikström, & Smart, 2007). Previous research in children propose a framework where attentional abilities are found to be the key factor to explain such differences (Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010; Söderlund et al., 2007). More attentive children are disturbed by noise, whereas inattentive children benefit from noise. The possibility that attention can be improved by the careful addition or reduction of external stimuli might be of great clinical significance. A similar framework for patients with VSN might have great impact in determining the appropriate rehabilitation approach.

We did not find differences in demographic or stroke characteristics between patients showing VSN on tests of different clusters. As for clinical characteristic, motor function (i.e., strength in upper and lower extremities, walking abilities, ADL dependence) was the only distinct factors between the patient groups, and was more impaired in patients who showed VSN on tests within the dynamic cluster (with or without VSN on test within the static cluster). Tests within the dynamic cluster do have stronger motor components compared to the paper-and-pencil tests within the static cluster, especially when it comes to motor strength. Even though motor impairment could hamper performance on a cancellation test, it is likely to have a larger impact on dressing (CBS) or moving through a corridor (MAC). Motor tasks require more attention when motor functions are impaired, which will likely compromise the simultaneous execution of a different task (e.g., detecting stimuli on the contralesional side of space) (Schaefer, 2014). For example, it is likely that attention for relevant stimuli while walking is lower for people who have motor impairment, as not falling or bumping has a higher priority. Our findings must be interpreted with caution given the small sample size of the group showing VSN on tests within the static cluster alone (n = 8). In addition, their z-score on the CBS was 2.82 (above the cut-off of 2, Figure 5.1), while their average z-score for the dynamic cluster was 1.06 (below the cut-off of 2, Table 5.1) when taken the MAC and simulated driving test into account. This indicates that this group did not purely show VSN on static tests alone. However, we used the average z-scores as this is similar to clinical practice, where a cognitive deficit is never diagnosed based on

the performance on one single test but instead, the complete picture of test results and observations is taken into account.

Strengths and limitations

A strength of this study is the large cohort of patients with VSN from whom we collected within-subject performances on an extensive selection of tests, including paper-and-pencil tests, an observational scale, a quantified test in a real-life environment, and a virtual reality test. A limitation of this study is the relatively selective sample of patients, namely patients who were admitted for inpatient rehabilitation care. In the Netherlands, patients are admitted for inpatient rehabilitation care when a safe discharge to home is not achievable from the hospital within 5 days. Patients should, however, be vital enough to participate in multidisciplinary therapy. In general, this patient population is relatively young and moderately impaired. For this reason, the current results might not generalize to an older and/or more severely impaired population. Furthermore, our sample of patients received inpatient rehabilitation including VSN treatment (one hour visual scanning training per week combined with ongoing feedback of nurses, occupational and physical therapists to enhance attention to the neglected side). Since the test session was conducted two weeks after admission, (spontaneous) recovery or successfully applied compensation strategies might have affected test performances.

Note, that the number and position of lines used in a line bisection task vary between studies. The line bisection test in our study was based on the Behavioural Inattention Test (Wilson et al., 1987). Participants were asked twice to bisect three lines that were presented in a staircase fashion across the screen (from lower left to the upper right). Previous research has shown differences in visuospatial attention in the left versus the right hemispace (Kesayan, Gasoyan, & Heilman, 2018; Ochando & Zago, 2018), as well as the upper versus the lower hemispace (Suavansri, Falchook, Williamson, & Heilman, 2012). In our study, we used the overall magnitude of the attentional bias (the average deviation of the six lines) without analysing the performances per line. Furthermore, most patients used their dominant hand (85% dextral) to perform the static tests on the tablet, yet four patients (all dextral) used their non-dominant hand as their stroke affected their dominant hand. Previous studies on pseudoneglect in neurologically healthy participants showed that handedness affected bisection errors, with dextral participants deviating slightly further to the left than sinistral participants (Jewell & McCourt, 2000). Leftward bisection errors are even more substantial when dextral subjects use their left (non-dominant) hand (MacLeod & Turnbull, 1999; Ochando & Zago, 2018). However, effects of pseudoneglect in neurologically healthy participants are much smaller than effects of VSN after stroke and, therefore, we do not expect that the hand used to bisect affected our results.

Clinical implications

We already know from extensive research and clinical insights that VSN is not easily assessed nor that designing a VSN test battery is an easy job, due to its heterogenic nature, complex manifestations, and fluctuations over time and tests. Several reviews have been published discussing the assessment of VSN (Bowen, McKenna, & Tallis, 1999; Menon & Korner-Bitensky, 2005; Plummer, Morris, & Dunai, 2003), its ecological validity (Azouvi, 2017), and the added value of computer-based testing (Schendel & Robertson, 2003) and Virtual Reality (Ogourtsova, Souza Silva, Archambault, & Lamontagne, 2017; Pedroli et al., 2015; Tsirlin et al., 2009). Consensus has only been reached on the fact that the assessment of VSN should always consist of several tests, as several tests are more likely to detect VSN. This study suggests the same, and again stresses the importance to include tests varying in levels of cognitive demand in order to capture VSN after stroke. Even though dynamic tests seem more challenging to be administered in patients with motor problems, it seems, based on our results, of great importance to test those patients in a dynamic manner. In patients with comorbidity, clinicians should administer VSN tests that specifically challenge the weakened abilities (e.g., motor, cognitive). Such tests would offer a more sensitive assessment of VSN in patients showing well-compensated or 'recovered' VSN on static paper-and-pencil tests.

Future research

We defined cognitive demand as the level of cognitive resources that are required to execute a task, varying as a function of task complexity (Tsaparli, 2014). Task complexity can be directly related to task features that increase information load, information diversity, or rate of information change, which determines the required cognitive demands (Campbell, 1988; Liu & Li, 2012). Furthermore, it is useful to distinguish between the objective and subjective task complexity, where the latter is defined as a function of the interaction between the task and task performer characteristics (e.g., knowledge, skills) (Liu & Li, 2012). In this study, we did not directly investigate objective or subjective task complexity and the related cognitive demand. By using an experimental paradigm, future research should focus on investigating cognitive demand by applying a staircase procedure to determine a threshold level of individual cognitive demand per test. This would provide more insight in the subtle difference between static and dynamic tests regarding the level of cognitive demand. The concepts of static and dynamic tests might then better be represented on a static-dynamic continuum with on one side static tests and on the other side dynamic tests with increasing levels of cognitive demand (Figure 5.3).

Furthermore, it might be useful to cluster tests of VSN based on other underlying concepts than the level of cognitive demand (e.g., clinical subtypes, involved cognitive processes).

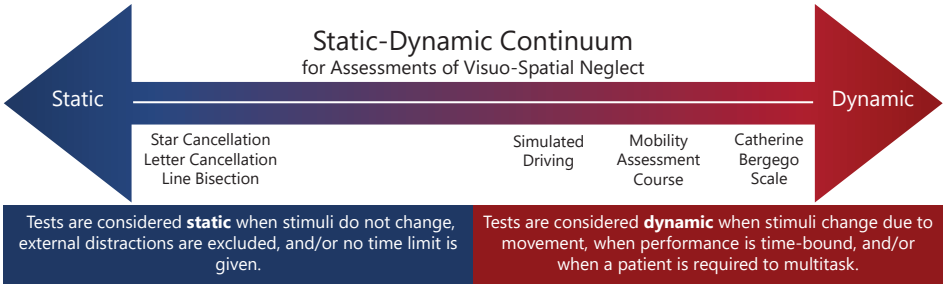

Figure 5.3. A hypothetical static-dynamic continuum of assessments of VSN with on the one side *static* tests with low levels of cognitive demands and on the other side *dynamic* tests with increasing levels of cognitive demand. Examples of tests used in the current study are shown on the continuum.

For instance, VSN is known as a heterogeneous syndrome involving different clinical subtypes that vary in modality (visual, auditory, or tactile), frame of reference (egocentric or allocentric) and region of space (personal, peripersonal or extrapersonal) (Corbetta, 2014; Rode, Pagliari, Huchon, Rossetti, & Pisella, 2016; Van der Stoep et al., 2013). Another well-known theoretical distinction of VSN is the perceptual-attentional VSN (patients fail to attend contralesional stimuli) or action-intention VSN (patients who are aware of contralesional stimuli, but fail to act on these stimuli) (Bartolomeo, D'Erme, Perri, & Gainotti, 1998). Each test targets a different clinical subtype, such as cancellation tests targeting peripersonal VSN and the CBS targeting peripersonal, extrapersonal as well as personal VSN (Azouvi et al., 2003; Menon & Korner-Bitensky, 2005; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2016). Other underlying concepts might be the different types of cognitive processes that are involved during a test. For instance, line bisection requires patients to estimate the size of an object, regardless of their location in reference to the individual (allocentric processes), while cancellation tasks requires visual search within a display of various stimuli (egocentric processes) (Ferber & Karnath, 2001; Van der Stigchel & Nijboer, 2018). Furthermore, stimuli on the contralesional side might not be perceived when stimuli are presented simultaneously on the ipsilesional side (i.e., extinction, suppression/reciprocal inhibition hypothesis) (Heilman, Valenstein, & Watson, 1984), which might be more often the case in dynamic tests due to more environmental distractors. Hence, the cognitive processes that are involved in our selection of static and dynamic tests differ between tests. Thus, even though we made clusters based on whether a test was static or dynamic, tests of VSN can also be clustered based on clinical subtypes or underlying cognitive processes that are involved while performing the tests. In a larger cohort of patients with VSN and by including more VSN tests, data-driven machine learning analyses might reveal which tests would cluster together. Data-driven analyses allow a generation of new hypotheses. This

would aid clinicians to gain a better understanding on how different tests of VSN relate to each other, and more importantly, a better understanding of VSN and its phenotypes. The choice of treatment could be based on this knowledge.

Finally, damage in several distinct brain regions has consistently been associated with VSN, such as several cortical and subcortical regions of the right hemisphere, including the middle and superior temporal gyrus, inferior parietal lobule, intraparietal sulcus, precuneus, middle occipital gyrus, caudate nucleus, and posterior insula, as well as in the white matter pathway corresponding to the posterior part of the superior longitudinal fasciculus (Molenberghs, Sale, & Mattingley, 2012). Different brain regions have been associated with impairments in different tests (Karnath & Rorden, 2012), and similarly, specific clinical subtypes of the VSN syndrome (Molenberghs et al., 2012). Future research could address whether damage in distinct brain regions might underly manifestations of VSN on static or dynamic tests.

Conclusions

In this study, we investigated the conceptual distinction between static and dynamic tests in a large cohort of patients with VSN. We found that manifestations of VSN may vary between patients, and in a given patient, according to the type of test that was used (static versus dynamic). Moreover, patients showing VSN on tests within the dynamic cluster had poorer motor function, poorer walking abilities and were more ADL dependent than patients showing VSN on the static cluster. Confirmatory factor analyses showed that the underlying factor structure corresponds to our proposed conceptual distinction between static and dynamic clusters of tests. As some patients show VSN on static tests but not on dynamic tests, and vice versa, we advise to include static paper-and-pencil tests as well as dynamic tests as part of a VSN battery in usual care. Future research involving experimental and data-driven approaches might result in a better understanding on how different tests of VSN relate to each other, and more importantly, a better understanding of VSN and its phenotypes.

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Appendix 5.1. Benjamini-Hochberg method

The Benjamini-Hochberg method consist of several steps: (1) put the individual *p*-values in order, from smallest to largest; (2) assign ranks to the *p*-values; (3) calculate each individual *p*-value's Benjamini-Hochberg critical value, using the formula (i/m)Q, where: *i* = the individual *p*-value's rank, *m* = total number of tests, *Q* = the false discovery rate (in our case .1); (4) compare the original *p*-values to the Benjamini-Hochberg critical values. Find the largest *p*-value that is less or equal to the critical value. All the *p*-values above are also significant.

Appendix 5.1a. Benjamini-Hochberg correction that is applied to the multiple comparisons of demographic and clinical characteristics between the groups

Comparisons	*p*-values	Rank	Benjamini-Hochberg critical value
Motricity Index upper	.005	1	(1/16) .10 = .006
Motricity Index lower	.011	2	(2/16) .10 = .013
Barthel Index	.018	3	(3/16) .10 = .019
Functional Ambulation Categories	**.025**	**4**	**(4/16) .10 = .025**
Days post stroke	.078	5	(5/16) .10 = .031
Lesion side	.078	6	(6/16) .10 = .038
Sex	.094	7	(7/16) .10 = .044
Stichting Afasie Nederland test	.225	8	(8/16) .10 = .05
Montreal Cognitive Assessment	.244	9	(9/16) .10 = .056
RAVLT Recognition	.322	10	(10/16) .10 =.063
RAVLT Immediate recall	.331	11	(11/16) .10 = .069
D-KEFS Tower test	.616	12	(12/16) .10 = .075
RAVLT Delayed recall	.666	13	(13/16) .10 =.081
Stroke type	.684	14	(14/16) .10 = .088
Age	.731	15	(15/16) .10 = .094
Level of education	.974	16	(16/16) .10 =.1

Note. The largest *p*-value ≤ critical value is depicted **in bold**. All the *p*-values above are also significant. **Abbreviations:** Rey Auditory Verbal Learning Test (RAVLT); Delis–Kaplan Executive Function System (D-KEFS).

Appendix 5.1b. Benjamini-Hochberg correction that is applied to the post-hoc Mann Whitney *U* tests for comparing the significant clinical characteristics (Motricity Index upper and lower, Barthel Index, Functional Ambulation Categories) between the groups

Comparisons (groups*)	***p*-values**	**Rank**	**Benjamini-Hochberg critical value**
Motricity Index upper (1–3)	.002	1	(1/12) .10 = .008
Motricity Index lower (1–3)	.003	2	(2/12) .10 = .017
Barthel Index (1–2)	.007	3	(3/12) .10 = .025
Motricity Index upper (1–2)	.007	4	(4/12) .10 = .033
Barthel Index (1–3)	.007	5	(5/12) .10 = .042
Motricity Index lower (1–2)	.014	6	(6/12) .10 = .05
Functional Ambulation Categories (1–3)	.015	7	(7/12) .10 = .058
Functional Ambulation Categories (1–2)	**.034**	**8**	**(8/12) .10 = .067**
Functional Ambulation Categories (2–3)	.189	9	(9/12) .10 = .075
Motricity Index lower (2–3)	.349	10	(10/12) .10 = .083
Motricity Index upper (2–3)	.524	11	(11/12) .10 = .092
Barthel Index (2–3)	.931	12	(12/12) .10 = .1

Note. The largest *p*-value ≤ critical value is depicted in bold. All the p-values above are also significant.
* Patient group that showed VSN on static cluster (group 1), Patient group that showed VSN on the dynamic cluster (group 2), Patient group that showed VSN on both the static and dynamic cluster (group 3).

In 2014, I came home from work and I started working om my assignment from my photography course. The next thing I remember is that I was wondering why the floor was so hard and cold. I had collapsed and when my wife walked in, she saw me lying on the floor. I wanted to reassure her that it was not a heart attack, but my speech was strange and I could not move the left side of my body. She called an ambulance which took me to the hospital. They told me I suffered from a stroke. After two weeks I was referred to a rehabilitation center. On my first day, I saw people shuffling through the hallway, that was hard for me. Initially, I only noticed the physical consequences of the stroke. When I was discharged home, I noticed that there were much more changes. In contact with my wife, I felt different mentally and emotionally. I never heard of the neglect syndrome before. On a test where I had to find objects on paper, I only found 19 objects out of 40 and missed the objects on the left. I learned compensation strategies during the rehabilitation trajectory, but my wife says I still miss things on my left side. I try to think about it, but I am not aware of what happens on my left. When I am riding my bike, I often drive too much to the left of the bicycle path. After the stroke, I quit my job and I retired early. I started doing different things, like attending a biology course. However, I had a hard time keeping up. I needed more repetition and I was not able to concentrate for a long time. I enjoyed participating in the research study. I was happy that I could help and do something useful. I always try to focus on what is possible, instead on what is not.

Chapter 6

Simulated driving: The added value of dynamic testing in the assessment of visuo-spatial neglect after stroke

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Abstract

Background: Visuo-spatial neglect (VSN) is generally assessed with neuropsychological paper-and-pencil tasks, which are often not sensitive enough to detect mild and/or well-compensated VSN. It is of utmost importance to develop dynamic tasks, resembling the dynamics of daily living.

Objective: A *simulated driving task* was used to assess (1) differences in performance (i.e., position on the road and magnitude of sway) between patients with left- and right-sided VSN, recovered VSN, without VSN and healthy participants; (2) the relation between average position and VSN severity; and (3) its diagnostic accuracy in relation to traditional tasks.

Methods: Stroke inpatients were tested with a cancellation task, the Catherine Bergego Scale and the simulated driving task.

Results: Patients with left-sided VSN and recovered VSN deviated more regarding position on the road compared to patients without VSN. The deviation was larger in patients with more severe VSN. Regarding diagnostic accuracy, 29% of recovered VSN patients and 6% of patients without VSN did show abnormal performance on the simulated driving task. The sensitivity was 52% for left-sided VSN. Right-sided VSN was not well detected, probably due to the asymmetric layout.

Conclusions: Based on these results, the simulated driving task should not be the only task to assess VSN, especially in its current form. Given the heterogenic nature of VSN, the assessment should always consist several tasks varying in nature and complexity and include a dynamic task to detect mild and/or recovered VSN. A symmetric design should be used when designing novel tasks to assess right-sided VSN.

Introduction

Visuo-spatial neglect (VSN) is a common cognitive disorder after stroke. VSN is defined as the inability to attend to, respond to, or orient toward novel stimuli presented in the contralesional space (Heilman, Valenstein, & Watson, 2000). This deficiency in *lateralized attention* is the core deficit of VSN (Buxbaum et al., 2004) and is usually measured with neuropsychological paper-and-pencil tasks. Left-sided VSN is more common (16–50%) than right-sided VSN (9–30%) and is more severe when measured with neuropsychological tasks (Chen, Hreha, Kong, & Barrett, 2015; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2016). The consequences in daily life activities are, however, largely comparable between left- and right-sided VSN (Ten Brink et al., 2016). VSN is associated with a slower and decreased functional and motor recovery (Chen et al., 2015; Nijboer, Kollen, & Kwakkel, 2014; Nijboer, van de Port, Schepers, Post, & Visser-Meily, 2013), resulting in prolonged hospitalization, safety risks, and a decreased chance of successful reintegration. For this reason, adequate assessment of VSN is important.

As mentioned above, VSN is generally assessed with neuropsychological paper-and-pencil tasks, such as cancellation, line bisection, and copying tasks. Although these tasks are convenient and easy to administer, research has often reported a lack of ecological validity and limitations in sensitivity (Pedroli, Serino, Cipresso, Pallavicini, & Riva, 2015; Ten Brink, Visser-Meily, & Nijboer, 2017; Tsirlin, Dupierrix, Chokron, Coquillart, & Ohlmann, 2009). During VSN treatment, patients are explicitly taught compensatory attentional strategies and consequently perform quite well on these static tasks with no time limit (Pedroli et al., 2015; Ten Brink et al., 2017). These tasks, therefore, do not capture mild deficits in lateralized attention that might only occur in dynamic daily life situations (e.g., walking on a busy sidewalk).

Complementary tasks have been developed, such as observational scales for clinicians. The Catherine Bergego Scale (CBS) is an example of a structured scale to observe VSN behaviour during daily activities, such as walking and eating (Azouvi et al., 2003; Ten Brink et al., 2013). The assignment of the scores, however, might vary significantly among clinicians due to differences in interpretation. In addition, the daily activities can not always be observed in one time period, by one therapist or in the same observational context (Chen, Hreha, Fortis, Goedert, & Barrett, 2012). Next to observational scales, investigators have developed ecologically valid multitasks (i.e., performing multiple operations simultaneously) conducted in the real world. As a real world environment continuously changes, the required responses also change (Pedroli et al., 2015; Rizzo, Schultheis, Kerns, & Mateer, 2004). This makes a task more demanding – or even in competition – for attentional processes (Ten Brink et al.,

2017). An example of such a task is the Mobility Assessment Course, where participants have to perform a wayfinding task in a corridor while detecting targets (Ten Brink et al., 2017). An important limitation is the lack of a standardized and controlled setting, which results in an inconsistent degree of distraction within or between assessments.

In recent years, promising new techniques like Virtual Reality (VR) have been used to simulate daily life situations in a safe and controlled manner (Rose, Brooks, & Rizzo, 2005; Tsirlin et al., 2009). By using VR simulations in neuropsychological assessment, new possibilities exist that go beyond paper-and-pencil tests. Researchers and clinicians can assess a patient's performance in a controlled and dynamic environment and predict the functional outcome based on those results.

Patients with VSN tend to deviate towards one side while walking. Previous research suggests that attention toward the ipsilesional side of space generally leads to contralesional deviations while navigating in real-life (Huitema et al., 2006; Turton et al., 2009). For example, patients with left-sided VSN tend to position themselves too close to walls on their left side, which often results in collisions into doorframes and objects (Turton et al., 2009). A recent study showed that patients with left-sided VSN allowed obstacles to be closer on their left side while walking down a virtual path, compared to obstacles on their right side (Houston et al., 2015). In the current study, a *simulated driving task* was used to detect this lateral deviation, and to investigate whether a dynamic task can detect VSN behaviour in patients who show well-compensated or even 'recovered' VSN on traditional tasks (i.e., shape cancellation task (SC) and/or CBS). This simulated driving task has already been used to investigate reaction time asymmetries in patients with VSN admitted for inpatient rehabilitation care (Van Kessel, Van Nes, Brouwer, Geurts, & Fasotti, 2010). However, this study included a small group of VSN patients ($n = 12$), and they did not investigate the navigational deviations. In our study, we investigated the differences in performance (i.e., position on the road, magnitude of sway) between patients with left- versus right-sided VSN, patients without VSN, and healthy control participants. The performance of patients with 'recovered' VSN, was compared with the performance of patients with and without VSN. Our second aim was to investigate the relation between the average position on the road, as a measure of lateralized attention, and VSN severity (measured with the SC and CBS). As a third aim, the diagnostic accuracy of the simulated driving task was assessed in relation to traditional VSN tasks. The sensitivity, specificity, positive, and negative predictive values were designated, in addition to the task's added value to the existing assessment of VSN.

Materials and methods

Participants

We included stroke patients who were admitted for inpatient rehabilitation care in *De Hoogstraat Rehabilitation Centre*, from August 2013 to February 2017. All stroke patients were screened for VSN within the first two weeks of admission. We recruited patients based on this screening. Some of the patients additionally participated in a randomized clinical trial (PAiR: #NTR3278; approved by the Medical Ethical Committee of the University Medical Centre Utrecht, #12-183/O) (Ten Brink, Visser-Meily, & Nijboer, 2015). In this RCT, only patients with VSN, indicated with the SC or CBS administered during the screening, were included. Inclusion criteria for the current study were: (1) clinical diagnosed stroke (confirmed by an MRI or CT scan); (2) age between 18 and 80 years old; and (3) sufficient comprehension and communication (evaluated by a neuropsychologist). Exclusion criteria were: (1) physically or mentally unable to participate; (2) no (complete) data on the simulated driving task; or (2) no data on the SC and CBS.

Finally, a healthy control group with a comparable age distribution was recruited. We excluded healthy controls with neurological or psychiatric disorder(s) in their previous medical history. All participants gave written informed consent. The experiment was performed in accordance with the Declaration of Helsinki. The research protocol was approved by the Medical Ethics Committee of De Hoogstraat Rehabilitation Centre.

Procedure

The VSN screening included, among other tasks, the SC and the CBS. The CBS was administered by the nursing staff separately (see 'Traditional VSN tasks' for task descriptions). The screening was part of usual care and took about 45 min in total. Approximately two weeks later, a second measurement containing the SC and the simulated driving task was conducted and took about 30 min. The CBS was only re-administered for patients with VSN who were also included in the randomized clinical trial (PAiR).

Simulated driving task

The simulated driving task (Van Kessel, Geurts, Brouwer, & Fasotti, 2013; Van Kessel et al., 2010) consisted of a driving scene projected on a large screen (2.13 m × 3.18 m; Figure 6.1). A straight road without intersections or oncoming traffic was projected on the screen. Participants were seated in front of the screen, which was placed at approximately 90 cm from their eyes. No car interior was projected, only a steering wheel was fixed on a table in front of the participant. A white plain board was placed on top of the table, to prevent

the participant from using the table as visuo-spatial reference. The simulated driving speed was approximately 50 km/hr at a fixed pace. Participants were instructed to use the steering wheel to maintain the starting position at the centre of the right lane, which is in line with Dutch road traffic regulations. Participants needed to adjust their position continuously, which was manipulated by simulated 'side wind' from both directions. When participants drove off the road into the left or right verge, the projection of the driving scene vibrated as a warning sign. No other feedback was given, to minimize interference with the task at hand. Prior to the task, the participant received a 1-min practice trial. The simulated driving task took 2 min.

Outcome measures consisted of the average position on the road and the average standard deviation of the position, as an indication of the magnitude of sway. Outcome measures were averaged every 15 s (i.e., 8 values in total). The total range of positions on the road (i.e., limited by the left and right verge) ranged between -600 (as virtual world distances) up to 200, with the position of 0 indicating the centre of the right lane.

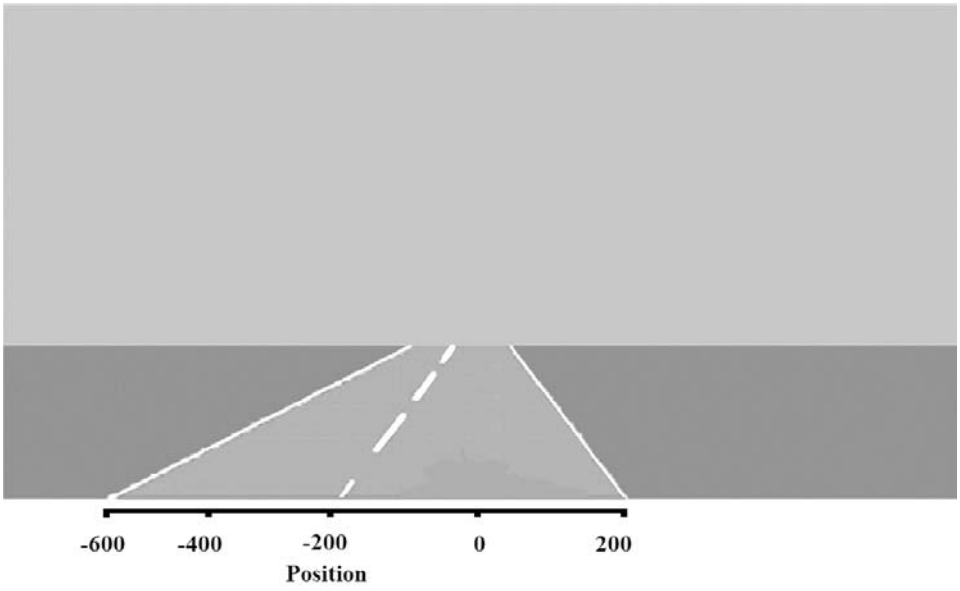


Figure 6.1. A schematic and achromatic overview of the driving scene (the display used in the current study was in colour).

Traditional VSN tasks

Shape cancellation task

A digitized SC, consisting of 54 targets (i.e., small shapes) and 75 distractors in different sizes (i.e., shapes, letters, and words) was used. Patients were instructed to cancel all targets. No time limit was given. After each designation a small circle appeared around the target and remained on screen. The asymmetry score (i.e., the difference in number of missed targets between the contralesional and ipsilesional side) was computed. An asymmetry score of two or more was considered as indicative for VSN (Van der Stoep et al., 2013). The asymmetry score was used to determine VSN severity (range between 0 and 27).

Catherine Bergego Scale

The CBS is an observation scale to assess VSN behaviour during basic activities of daily living. The nursing staff observed and rated behaviour during 10 activities (e.g., dressing or eating) with a score of 0 (no VSN) to 3 (severe VSN). For computing the total score, we corrected for missing items (e.g., because patients were unable to independently perform the activity or the situation was not observed). The total score was the sum of the item scores, divided by the number of valid items, multiplied by 10 (resulting in a total score ranging from 0 [no VSN] to 30 [severe VSN]). A total score of ≥ 6 was considered as indicative for VSN (Azouvi et al., 2003; Ten Brink et al., 2013).

Demographic and clinical characteristics

We collected data on sex, age, and level of education from the medical files. Level of education was assessed using a Dutch classification system (Verhage, 1965), that consists of seven levels, with 1 being the lowest (less than primary school) and 7 being the highest (academic degree). These levels were converted into three categories for analysis: low (Verhage 1–4), average (Verhage 5), and high (Verhage 6–7). Additionally, we extracted the following characteristics from the medical files: days post-stroke onset, stroke type (i.e., ischaemic, haemorrhage, or subarachnoid haemorrhage), the presence of language or communication deficits measured with the Stichting Afasie Nederland (SAN) score (Deelman, Koning-Haanstra, Liebrand, & Van den Burg, 1981), the level of independence during daily life activities measured with the Barthel Index (Collin, Wade, Davies, & Horne, 1988), and the level of motor strength of upper and lower extremities measured with the Motricity Index (Collin & Wade, 1990). Global cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), or the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). In order to create one score for global cognitive functioning, the MMSE

scores were converted into a MoCA score by using the following formula: MoCA = (1.124 × MMSE) – 8.165 (Solomon et al., 2014).

Statistical analyses

Categorization of patients

We categorized patients based on their performance on the SC and the CBS during the VSN screening and the second measurement. If there was a discrepancy concerning VSN side between the CBS and the SC, the patient was excluded. Patients who showed left-sided VSN on the SC and/or the CBS during the screening and second measurement, were assigned to the stroke group with left-sided VSN (left-sided VSN+). Patients who showed right-sided VSN on the SC and/or the CBS during the screening and second measurement, were assigned to the stroke group with right-sided VSN (right-sided VSN+). Patients who showed left-sided VSN during the screening, but not on the second measurement, were referred to as the recovered group (left-sided R-VSN). Patients who showed right-sided VSN during the screening, but not on the second measurement, were referred to as the recovered group (right-sided R-VSN). However, right-sided R-VSN patients were excluded because of a small sample size (n = 2). Patients who did not show VSN on both measurements were assigned to the group without VSN (VSN-).

Demographic and clinical characteristics

Non-parametric tests (Kruskal-Wallis non-parametric ANOVA and post-hoc Mann-Whitney U test for continuous variables, and Chi-square test for categorical variables) were used to compare demographic and clinical characteristics between the five groups (i.e., [1] left-sided VSN+, [2] right-sided VSN+, [3] left-sided R-VSN, [4] VSN- and [5] healthy control participants). For the post-hoc tests, a Bonferroni correction was applied to counteract the problem of multiple comparisons.

Differences between groups on the simulated driving task

Mann-Whitney U tests were used to compare the average position on the road and the magnitude of sway between left-sided VSN+, right-sided VSN+, VSN- patients. VSN- patients were compared to healthy control participants (adjusted p for four tests = .013). To investigate the performance of left-sided R-VSN patients, we compared their performance with left-sided VSN+ and VSN- patients (adjusted p for two tests = .025).

Relation with VSN severity

Spearman correlations between the average position on the road (absolute) and VSN severity (SC asymmetry score [absolute] and CBS total score) were computed. We used the absolute values in order to be able to analyse combined data of patients with left- and right-sided VSN. An *r* of .1 was considered a small, .3 a moderate, and .5 a large relation (Field, 2009). The level of significance was set at $p = .05$.

Diagnostic accuracy

The normal range was computed based on the performance of 21 healthy control participants. An SD of 2 above and below the average position was used to define the normal range. The average position on the road of the healthy control participants was -16.73 (SD = 42.39), resulting in a normal range of -101.51 to 68.05.

Furthermore, we calculated the sensitivity, specificity, positive predictive value (i.e., the probability that a patient with an average position outside normal range did have VSN, based on the SC and/or CBS), and the negative predictive value (i.e., the probability that a patient with an average position within normal range did not have VSN, based on SC and/or CBS). To determine the added value, we provided the percentages of left-sided R-VSN and VSN- patients, who performed outside normal range on the simulated driving task.

Finally, Receiver Operating Characteristic (ROC) curves were constructed by computing the sensitivity and specificity of the average position in predicting VSN for the following groups: left-sided VSN+ and right-sided VSN+.

Results

A total of 138 stroke patients were recruited. For the current study, 38 patients were excluded due to the following reasons: (1) no data on the simulated driving task ($n = 13$), (2) no data on the SC and CBS ($n = 10$), (3) right-sided R-VSN patients because of the small sample size ($n = 2$), and (4) discrepancy between affected side (left/right) based on the SC and CBS ($n = 13$). In addition, 36 healthy control participants were recruited, but 15 participants were excluded due to the following reasons: (1) no data on simulated driving task ($n = 4$), and (2) < 30 years old ($n = 11$). In total, 33 patients with left-sided VSN+, 7 patients with right-sided VSN+, 7 patients with left-sided R-VSN, 53 without VSN and 21 healthy control participants were included.

Demographic and clinical characteristics

Demographic and clinical characteristics are reported in Table 6.1. Most patients showed contralesional VSN (left-sided VSN due to right hemispheric damage, and right-sided VSN due to left hemispheric damage). One patient with recovered left-sided VSN had left hemispheric damage (ipsilesional VSN). Three patients had bilateral lesions.

Statistical comparisons were conducted between the five groups (i.e., left-sided VSN+, right-sided VSN+, left-sided R-VSN, VSN-, and healthy control participants). There was a significant difference in time post stroke, the presence of language or communication deficits, independence in daily life and motor strength of upper and lower extremities between the patients groups. The *post-hoc* tests (adjusted $p = .008$) showed that the time after stroke was higher for left-sided VSN+ patients compared to VSN- patients ($U = 497.00$, $z = -3.35$, $p = .001$). Compared to VSN- patients, left-sided VSN+ patients had a lower motor strength of upper and lower extremities (arm: $U = 214.00$, $z = -3.89$, $p < .001$[1]; leg: $U = 298.00$, $z = -2.81$, $p = .005$). Compared to left-sided VSN+ patients, right-sided VSN+ patients had more language and communication deficits ($U = 20.50$, $z = -3.27$, $p = .001$). Also, VSN- patients were more independent in basic daily activities compared to left-sided VSN+ patients ($U = 190.50$, $z = -5.21$, $p < .001$) and right-sided VSN+ patients ($U = 32.50$, $z = -3.22$, $p = .001$).

Differences between groups on the simulated driving task

Left-sided VSN+, right-sided VSN+, VSN-, and healthy control participants

The average position of left-sided VSN+ patients deviated more ($M = -125.75$) compared to VSN- patients ($M = -11.75$; $U = 315.00$, $z = -4.97$, $p < .001$, $r = -.54$) and compared to right-sided VSN+ patients ($M = 0.57$; $U = 41.00$, $z = -2.65$, $p = .008$, $r = -.42$). The average position on the road did not differ significantly between right-sided VSN+ and VSN- patients ($U = 142.00$, $z = -1.00$, $p = .316$, $r = -.13$). The average position of VSN- patients and healthy controls ($M = -16.73$) did not differ significantly ($U = 512.50$, $z = -.53$, $p = .598$, $r = -.07$). See Figure 6.2a.

Likewise, left-sided VSN+ patients showed a larger magnitude of sway ($M = 68.45$) compared to VSN- patients ($M = 32.48$; $U = 276.00$, $z = -5.32$, $p < .001$, $r = -.57$) and right-sided VSN+ patients ($M = 36.66$; $U = 45.00$, $z = -2.51$, $p = .012$, $r = -.40$). The magnitude of sway did not differ significantly between right-sided VSN+ patients and VSN- patients ($U = 130.50$,

[1] We tested the relation between the average position on the road (absolute) and motor strength in the upper extremities. We did not found a significant relation within the left-sided VSN+ patients ($rs = -.29$, $p = .168$), right-sided VSN+ patients ($rs = -.68$, $p = .140$), left-sided R-VSN patients ($rs = .30$, $p = .624$), and VSN-patients ($rs = .03$, $p = .842$).

Table 6.1. Demographic and characteristics, means (SD) or percentages split per group

	Left-sided VSN+ (n = 33)	***n***	**Right-sided VSN+** (n = 7)	***n***	**Left-sided R-VSN** (n = 7)	***n***	**VSN-** (n = 53)	***n***	**Healthy** (n = 21)	***n***	**Statistics**
Sex (% male)	66.7	33	85.7	7	57.1	7	75.5	53	52.4	21	$\chi^2(4) = 5.16$, $p = .271$
Age (years)	58.83 (9.18)	33	54.75 (11.48)	7	54.47 (14.69)	7	58.86 (12.14)	53	58.77 (9.86)	21	$H(4) = 1.21$, $p = .877$[a]
Level of education (%)		33		6		7		51		21	$\chi^2(8) = 12.99$, $p = .112$
Low	27.3		50		14.3		23.5		0		
Moderate	36.4		33.3		42.9		29.4		28.6		
High	36.4		16.7		42.9		47.1		71.4		
Time post stroke (days)	60.36 (31.83)	33	43.00 (26.54	7	50.00 (37.76)	7	41.89 (39.77)	53			$H(3) = 11.49$, $p = .009$
Stroke type (%)		26		6		6		39			$\chi^2(6) = 4.47$, $p = .613$
Ischemic	76.9		66.7		66.7		84.6				
Haemorrhage	15.4		33.3		33.3		10.3				
SAH	7.7		0		0		5.1				
Lesion side (%)[b]		32		7		7		28			
Left	0		71.4		14.3		59.6				
Right	96.9		0		85.7		36.2				
Bilateral	3.1		28.6		0		4.3				
SAN (1–7)	6.23 (1.06)	26	2.93 (2.09)	7	5.86 (1.86)	7	5.40 (1.68)	40			$H(3) = 13.36$, $p = .004$
BI (0–20)	7.92 (4.83)	33	7.86 (3.89)	7	11.14 (3.24)	7	14.90 (4.51)	40			$H(3) = 33.29$, $p < .001$
MI arm (0–100)	41.13 (41.29)	24	28.67 (45.28)	6	57.40 (37.16)	5	81.00 (28.21)	41			$H(3) = 19.14$, $p < .001$
MI leg (0–100)	51.71 (38.57)	24	40.43 (41.77)	7	67.83 (35.29)	6	77.38 (27.96)	42			$H(3) = 11.04$, $p = .012$
MoCA (0–30)	19.59 (4.50)	28	16.73 (7.63)	4	23.46 (1.98)	6	22.24 (5.10)	34			$H(3) = 10.25$, $p = .017$
CBS (0–30)	18.94 (7.32)	33	14.49 (4.13)	7	13.99 (6.22)	7	.66 (1.22)	53			
SC (0–27)	9.31 (7.61)	32	1.83 (3.13)	6	1.29 (1.38)	7	.25 (.43)	53			

Notes. BI = Barthel Index; MI = Motricity Index; MoCA = Montreal Cognitive Assessment; SAH = subarachnoid haemorrhage; SAN = Stichting Afasie Nederland.
a) We tested the relation between the average position on the road (absolute) and age. We did not found a significant relation within the left-sided VSN+ patients (rs = .10, p = .585), right-sided VSN+ patients (rs = -.11, p = .819), left-sided R-VSN patients (rs = .29, p = .535), VSN-patients (rs = .16, p = .265) and healthy control participants (rs = .15, p = .507). b) Most patients showed contralesional VSN, except for one patient showing ipsilesional VSN. Three patients had bilateral lesions.

z = -1.27, p = .205, r = -.16). The magnitude of sway did not differ significantly between VSN- patients and healthy controls (M = 27.51; U = 389.50, z = -2.00, p = .045, r = -.23). See Figure 6.2b.

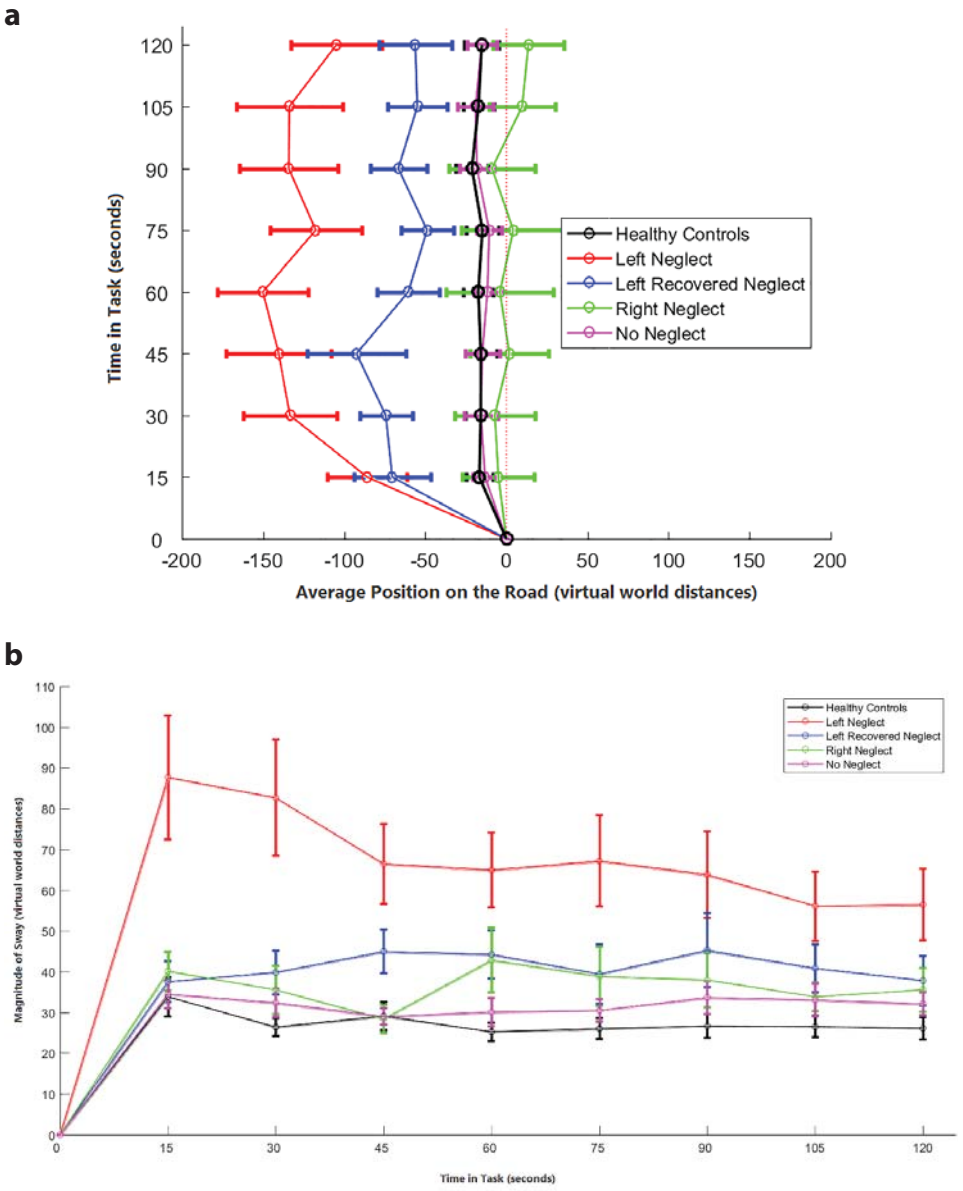


Figure 6.2. Overview of the **(a)** average position on the road, and **(b)** average magnitude of sway for left-sided VSN+, right-sided VSN+, left-sided R-VSN, VSN- patients and healthy control participants. The error bars represent the variability (standard deviation) in the average position or sway. With regard to Figure 6.2A, the dashed line represents the starting position at the centre of the right lane.

Left-sided VSN+, left-sided recovered VSN and VSN-

The average position on the road of left-sided R-VSN patients (M = -65.46) did not significantly differ from the position of left-sided VSN+ patients (U = 76.50, z = -1.39, p = .165, r = -.22). However, left-sided R-VSN deviated more to the left compared to VSN- patients (U = 79.00, z = -2.45, p = .014, r = -.32).

The magnitude of sway in left-sided R-VSN patients (M = 41.27) did not significantly differ from the sway in left-sided VSN+ patients (U = 63.00, z = -1.87, p = .062, r = -.30), nor from the sway of VSN- patients (U = 115.50, z = -1.61, p = .107, r = -.21).

Relation with VSN severity

There was a moderate positive relation between the average position and VSN severity as measured with the SC (rs = .47, p < .001; Figure 6.3a). A high positive correlation was found between the average position and VSN severity as measured with the CBS (rs = .53, p < .001; Figure 6.3b).

a

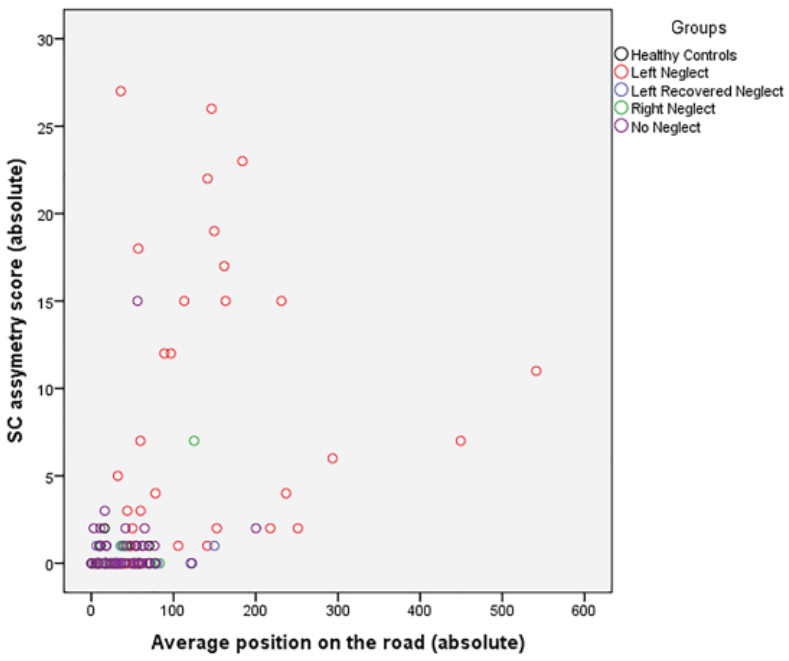


Figure 6.3. The average position on the road and its relation with VSN severity measured with **(a)** SC asymmetry score; and **(b)** CBS total score.

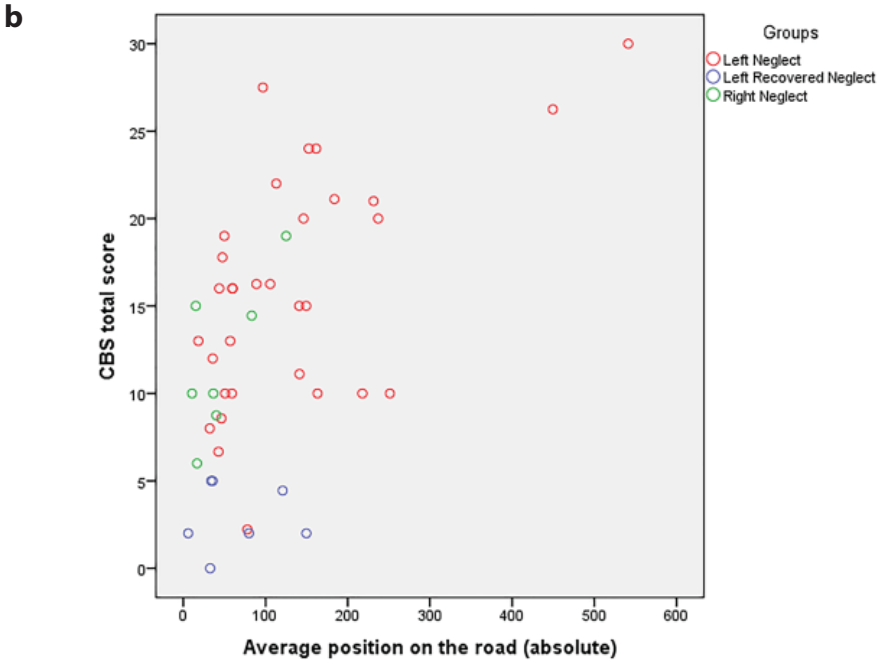


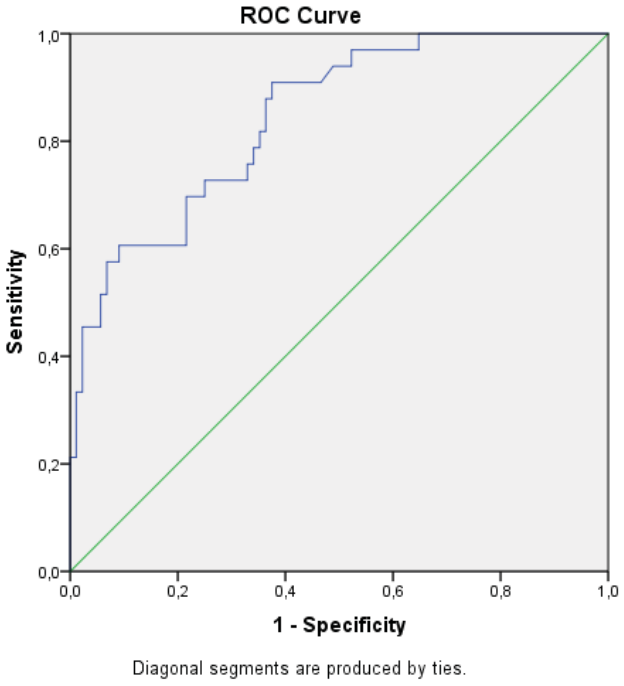
Figure 6.3. *Continued.*

Diagnostic accuracy

With respect to sensitivity, 51.5% of left-sided VSN+ patients and 28.6% of right-sided VSN+ patients performed outside the normal range regarding the position on the road. With respect to specificity, 94.3% of VSN- patients performed within normal range. Regarding left-sided VSN, the positive predictive value was 85%, and the negative predictive value was 75.8%. Regarding right-sided VSN, the positive predictive value was 40%, and the negative predictive value was 90.9%. Of the left-sided R-VSN patients, 28.6% performed outside normal range on the simulated driving task. Regarding VSN- patients, 5.7% performed outside normal range.

A ROC curve was computed for left-sided VSN+ and right-sided VSN+ patients. We found that the simulating driving task was more accurately as an assessment tool for left-sided VSN+ patients (area under the curve = .844) compared to right-sided VSN+ patients (area under the curve = .429; Figure 6.4).

a



b

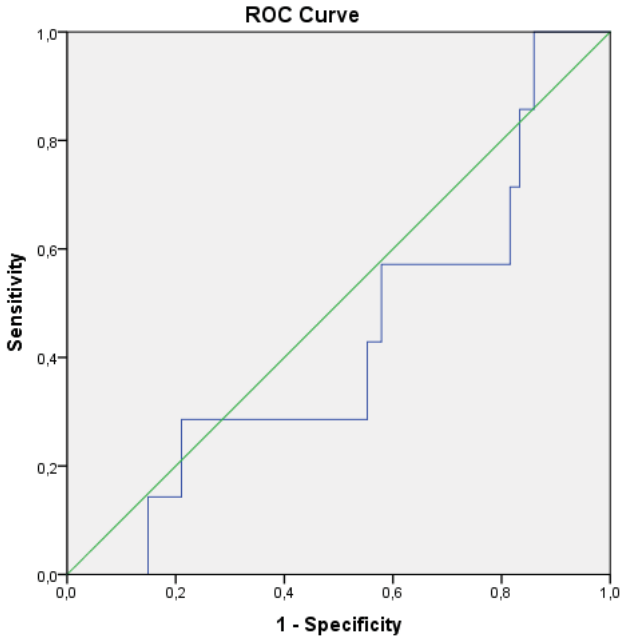


Figure 6.4. ROC curve for average position on the road for **(a)** left-sided VSN+ patients; **(b)** right-sided VSN+ patients.

Discussion

The aims of the current study were threefold: (1) to assess differences in performance (i.e., position on the road, magnitude of sway) on a simulated driving task between patients with left-sided VSN, right-sided VSN, 'recovered' left-sided VSN, without VSN and healthy control participants; (2) to investigate the relation between the average position and VSN severity; and (3) to assess the diagnostic accuracy of the simulated driving task in relation to traditional VSN tasks.

With respect to the first aim, left-sided VSN+ patients showed a larger magnitude of sway compared to VSN- patients and tended to deviate more to the left side of the right lane, even up to the left verge. This leftward deviation is in line with previous findings that attention toward the ipsilesional side may lead to contralesional deviations (Houston et al., 2015; Huitema et al., 2006; Turton et al., 2009). The position of right-sided VSN+ patients was comparable with the position of VSN- patients. This is likely the result of the asymmetric layout of the simulated driving task. There were only two lanes demarcated by two verges. Patients started in the centre of the right lane. As a result, there was less room for the expected rightward deviation. Also, a relatively small deviation towards the right, in the right verge, was directly interrupted with the warning sign. The ROC curve analyses supported this finding, as we found that the simulating driving task is a more accurate assessment tool for left-sided VSN compared to right-sided VSN. In future research, a symmetric design should be used to enhance the probability to detect right-sided VSN. The average position on the road of left-sided recovered VSN patients was of intermediary level between the positions on the road of left-sided VSN+ and VSN- patients. The 'recovered' patients deviated significantly more from the centre compared to VSN- patients. Other studies also reported persistent VSN behaviour in patients showing 'recovered' VSN on paper-and-pencil tasks (Buxbaum et al., 2004; Houston et al., 2015; Ten Brink et al., 2017). These results fit the clinical observations that neuropsychological paper-and-pencil tasks are not always sensitive enough to assess mild or well-compensated VSN. This is probably due to the lack of multitasking, attentional engagement, distractions, and/or time limit (Azouvi, 2017; Bonato, 2012, 2015; Ten Brink et al., 2017). Furthermore, the ability to reorient attention contralesionally may recover rather quickly, but the ipsilesional attention bias may be relatively persistent (Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994). Regaining the ability to reorient contralesionally may explain why 'recovered' VSN patients do well on static paper-and-pencil tasks. In our study, it is possible that the remaining ipsilesional attention bias in 'recovered' VSN patients might cause the deviation to the contralesional side as the simulated driving task might be more demanding for attentional processes. Also, attention towards the ipsilesional side leads to contralesional deviations while navigating in dynamic, real-life situations (Houston et

al., 2015; Huitema et al., 2006; Turton et al., 2009). A note of caution is due here since we cannot state which underlying process causes the effect of the 'recovered' VSN patients in our study. This is an important issue for future research, as well as determining which factors (e.g., clinical severity of stroke (Nijboer, Winters, Kollen, & Kwakkel, 2018), specific white-matter disconnections (Lunven et al., 2015), but also demographic factors and comorbid conditions (Kwakkel et al., 2017)) predict the recovery of VSN measured with different measures (static versus dynamic).

As for the second objective, a moderate positive relation was found between VSN severity as measured with a paper-and-pencil task (SC) and the average position on the road, indicating that more severe VSN was related to a more deviant position. A strong positive relation was found between VSN severity as measured with an observational scale (CBS) and the average position. As both the CBS and simulated driving task are more dynamic in nature than the SC, this finding suggests that dynamic tasks, like the simulated driving task, demand more natural behaviour and consequently relate more to daily activities (Tsirlin et al., 2009). Also, by using dynamic tasks in neuropsychological assessment, the results have a greater clinical relevance because of the enhanced ecological validity, and could subsequently be a first step for the development of effective functional rehabilitation approaches (Schultheis, Himelstein, & Rizzo, 2002).

With respect to the third aim, the sensitivity was 52% for left-sided VSN and 29% for right-sided VSN, and the specificity was 94%. The positive predictive value for left-sided VSN was 85% and right-sided VSN 40%. The negative predictive value for left-sided VSN was 76% and right-sided VSN 91%. Based on these findings, the simulated driving task cannot be used in isolation to detect VSN. For example, a percentage of patients do show VSN on the SC and/or CBS, but not on the simulated driving task (49% of left-sided VSN and 71% of right-sided VSN patients). Similar percentages are found when patients are categorized based on the SC and CBS separately, indicating that approximately 50% of patients show VSN on a dynamic task irrespectively of the test you use to categorize them. For this reason, the assessment of VSN should always consist of more than a single task and, ideally, of several tasks varying in nature and complexity (Azouvi et al., 2006). Additionally, the assessment of VSN should include dynamic tasks with an improved ecological validity. When developing such a test battery, it is important to investigate whether a new test improves the diagnostic accuracy by going beyond the available diagnostic information from traditional tests (Moons, De Groot, Linnet, Reitsma, & Bossuyt, 2012). Therefore, the most important clinically relevant finding of the current study was the added value of the simulated driving task. In a sequence of steps, diagnostic information has been documented: first using a widely used cancellation task (SC) and observational scale (CBS), and second using a simulated driving task as the

dynamic counterpart. In total, 29% of patients, who showed left-sided recovered VSN on a paper-and-pencil task and during observations through daily activities, still showed abnormal performance on the simulated driving task. This finding shows the 'clinical utility' (Bossuyt, Reitsma, Linnet, & Moons, 2012) of dynamic testing, as the use of the simulated driving task can identify more patients who will benefit from the necessary treatment. Likewise, an additional 6% of patients not showing VSN on the SC and CBS, did show abnormal performance on the simulated driving task. Although the sample sizes are rather small, this study shows that the addition of a dynamic task, such as a 2-minute simulated driving task, might improve the diagnostic accuracy of the existing clinical pathway for detecting VSN.

Previous research emphasized the need for divers dynamic tasks, resembling real-life, because paper-and-pencil tasks are often not sensitive enough to detect mild and/or well-compensated VSN (Appelros, Nydevik, Karlsson, Thorwalls, & Seiger, 2003). In dynamic tasks there is (moving) interference of stimuli or time pressure, in which stimuli are presented for a short period of time. An example is the Mobility Assessment Course (MAC). Such tasks can be more sensitive for the lateralized attention deficit compared to paper-and-pencil tasks (Ten Brink et al., 2017). Regarding the MAC, 10–19% of patients without VSN on paper-and-pencil tasks showed VSN behaviour on the MAC. This task, however, lacks standardization and experimental control. For the assessment of VSN, we need tasks that are dynamic and ecologically valid but also consist a controlled setting to purely measure lateralized inattention. The simulated driving task is such an example, because of the high level of control that enables a consistent presentation of stimuli, and increases standardization of the task (Rizzo et al., 2004). Hence, fluctuations in performance can additionally be measured during the task, but also in the course of rehabilitation, because of the consistency across assessments. Previous studies with VSN patients have reported inconsistency in performance throughout the day (Corbetta, 2014) and during the period of recovery (Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007). The simulated driving task could serve as dynamic task to assess mild VSN and to further explore fluctuations in performance among VSN patients.

Another reason to extend the traditional assessment of VSN with dynamic tasks, is the heterogeneity of the VSN syndrome and its divers manifestation (Appelros et al., 2003; Corbetta, 2014). Some patients may perform within normal range with respect to the primary outcome measures on paper-and-pencil tasks, but show VSN when measured with dynamic tasks, and vice versa. The latter finding (i.e., showing VSN on static, paper-and-pencil tasks while performing normally on a dynamic, driving task) seems counterintuitive, as a more dynamic situation likely demands more attention. It could be explained by *stochastic*

resonance, which describes the phenomena where 'noise' (e.g., additional visual, auditory, tactile stimuli) can enhance or decrease sensory information processing and perception (Moss, Ward, & Sannita, 2004). In other words, some patients benefit from additional stimuli, and subsequently perform better in a dynamic environment, whereas others do not. Thus, the nature of the task (static versus dynamic) can cause differences in performance. Furthermore, the heterogeneity of VSN also extends to modality (i.e., visual, auditory or tactile), frame of reference (i.e., egocentric or allocentric), or region of space (i.e., peripersonal or extrapersonal) (Corbetta, 2014; Rode, Pagliari, Huchon, Rossetti, & Pisella, 2016; Van der Stoep et al., 2013). With the simulated driving task, we only measured lateralized visuospatial inattention. It can be concluded, that the assessment of VSN should not consist of one single task, but should always consist of several tasks to detect all VSN patients.

Strengths and limitations

A strength of this study is the use of a dynamic task in a stroke population in the sub-acute phase of rehabilitation. Accurate assessment in an early phase is of utmost importance to provide the necessary information to determine the appropriate approach for rehabilitation. Administration of the simulated driving task, as part of neuropsychological assessment, was feasible, as all patients were able to perform this task. Even patients with lower motor strength were able to perform this task with one hand without negatively affecting the position on the road (i.e., the main outcome measure for VSN). Also, the inclusion of the different subgroups (left-sided VSN+, right-sided VSN+, left-sided R-recovered) can be considered as a strength, as it allows an in-depth exploration of VSN.

An important limitation of the task was the asymmetric layout, that should be adjusted before it can be used to detect right-sided VSN patients. Previous research has emphasized the necessity of accurate assessment tools to detect right-sided VSN, as right-sided VSN is often not detected when measured with paper-and-pencil tasks (Ten Brink et al., 2016). Consequences in daily life, however, are similar to left-sided VSN patients, and accurate diagnosis is, therefore, of great importance. Hence, a symmetric design should be used when designing novel tasks to assess VSN. In addition, other visual field deficits, such as hemianopia, might also result in a deviated position on a driving task (Bowers, Mandel, Goldstein, & Peli, 2010; Wood et al., 2011). No systematic screening for hemianopia was done in the rehabilitation centre nor in the VSN screening, so it remains unclear whether hemianopia was present in a subset of stroke patients. Based on the scores of the tests, the observations during activities of daily living, and the inspection of the MRI scans in a subset of patients, however, we are convinced that it is highly unlikely that hemianopia has had a major influence on the current results. The SC measures inattention, and patients

with hemianopia usually use compensatory strategies and find all targets in this phase post-stroke onset. Furthermore, the nurses who filled in the CBS were instructed to score VSN behaviour only and no behaviours due to other sensory deficits (including visual field defects). Regarding the simulated driving task, it is highly unlikely that hemianopia might be a potential cofounder. Hemianopic patients tend to deviate toward their seeing field, thus, in the opposite direction to that of VSN patients (Bowers et al., 2010; Wood et al., 2011). If anything, therefore, hemianopic patients in the VSN sample would have weaken the results.

Finally, we would like to stress that the current test is not intended for assessing fitness-to-drive after stroke. This simulated driving task did not represent the complexity of real-life, because of its relatively 'simple' design (e.g., the lack of intersections and oncoming traffic, and the limited driving operations the user had to encounter). Nevertheless, even though this task was not intended to assess traffic participation, VR simulations can play an important role for such an assessment after stroke. A recent study used a driving simulator involving various traffic-based events to assess fitness-to-drive in stroke patients (Blane, Falkmer, Lee, & Dukic Willstrand, 2017). In future research, substantial adaptations need to be made with regard to the current simulated driving task in order to design a suitable VR simulation to these aims. Also, in the simulated driving task, the outcome measures were averaged every 15 s (resulting in 8 values in total). In future research, a continuous data acquisition would give more detailed and precise information, and could subsequently give insight in the exact timing of onset of deviations, stabilization of lane position, and time-dependent changes.

Conclusions

This study proposes a dynamic task as supplement to improve the diagnostic accuracy of the existing clinical pathway, and consequently detect more VSN patients who can benefit from VSN treatment during rehabilitation. An extra 6–29% of patients who did not show VSN on a paper-and-pencil task nor on an observational scale, did show VSN behaviour on a simple 2-min simulated driving task. It is important to note that this conclusion is based on a rather small sample. The sensitivity was 52% for left-sided VSN. Right-sided VSN was not well detected, probably due to the asymmetric layout. Based on these results, the simulated driving task should not be used in isolation to assess VSN, especially in its current form. Given the heterogenic nature of VSN, the assessment should always consist several tasks varying in nature and complexity and include a dynamic task to detect mild and/or recovered VSN.

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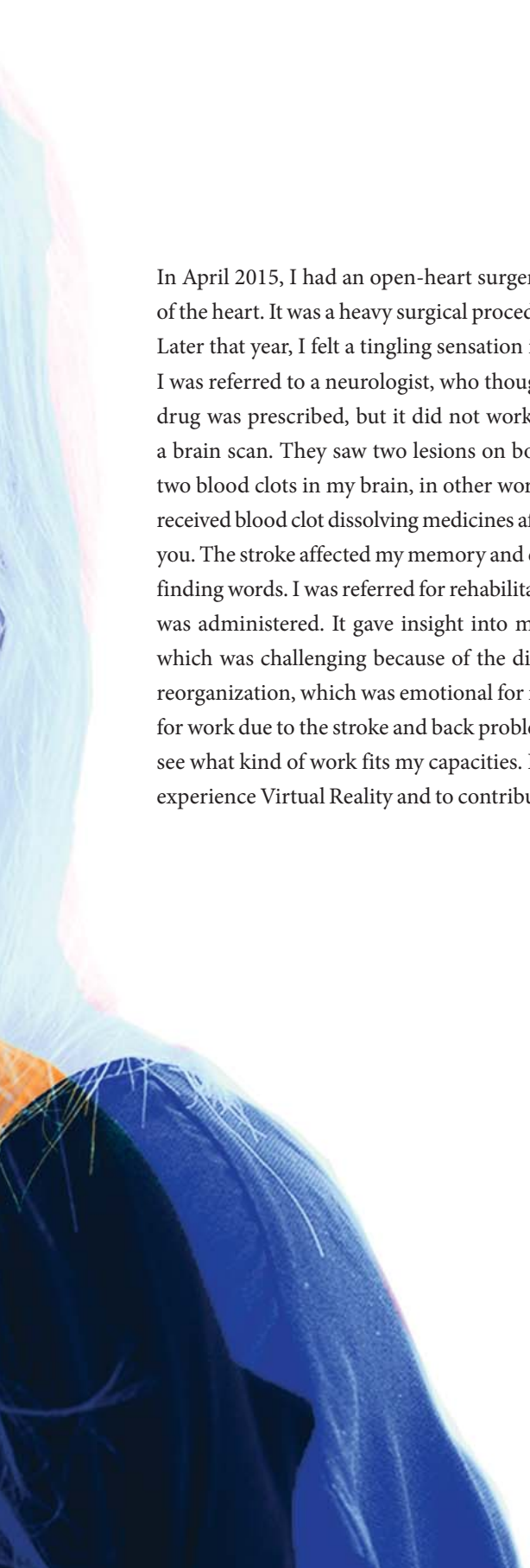

In April 2015, I had an open-heart surgery to replace part of the aorta and the aortic valve of the heart. It was a heavy surgical procedure, but it went well and I recovered quite quickly. Later that year, I felt a tingling sensation in my arms, which came back several times a day. I was referred to a neurologist, who thought I had some form of epilepsy. An anti-epileptic drug was prescribed, but it did not work. I asked for a second opinion and they initiated a brain scan. They saw two lesions on both side of my brain. The aortic valve had caused two blood clots in my brain, in other words a stroke. I felt frightened that it happened, as I received blood clot dissolving medicines after the surgery. You do not expect this to happen to you. The stroke affected my memory and energy level and I had difficulty concentrating and finding words. I was referred for rehabilitation care, where a neuropsychological assessment was administered. It gave insight into my functioning. I returned back to work in 2017, which was challenging because of the difficulties I had. I eventually lost my job due to a reorganization, which was emotional for me. In 2018, I was declared partially incapacitated for work due to the stroke and back problems. I am currently in a reintegration trajectory to see what kind of work fits my capacities. I participated in the research, because I wanted to experience Virtual Reality and to contribute to the expansion of knowledge about the brain.

Chapter 7

Feasibility and user-experience of virtual reality in neuropsychological assessment following stroke

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Abstract

Virtual Reality (VR) offers the possibility to assess cognitive functioning in a dynamic environment resembling daily life. In this cross-sectional study, we used two user interfaces, namely non-immersive VR by using a computer monitor (CM) and immersive VR by using a head-mounted display (HMD). We investigated (1) potential differences in feasibility, user-experience, and a potential preference for one user interface over another between stroke patients and healthy controls; (2) potential differences in feasibility, user-experience, and preference between patients referred for *inpatient* rehabilitation care and patients referred for *outpatient* rehabilitation care; and (3) potential demographic and clinical characteristics that were related to patients' preference for one user interface over another. Stroke patients (n = 88) and healthy controls (n = 66) performed a VR-task with a CM and HMD. Both user interfaces were feasible to use, irrespective of clinical referral (in- or outpatient rehabilitation care). Patients reported an enhanced feeling of engagement, transportation, flow, and presence, but more negative side effects when tested with a HMD, compared to a CM. The majority of stroke patients had no preference for one user interface over the other, yet younger patients tended to prefer a HMD. VR seems highly feasible in stroke patients.

Introduction

Cognitive rehabilitation refers to a set of interventions that focus on improving cognitive functioning to promote functional independence during activities of daily living (ADL) and social participation (Cicerone et al., 2000). Cognitive rehabilitation typically begins with a thorough neuropsychological assessment to identify cognitive strengths and weaknesses. The conclusions of the assessment are used to formulate an appropriate treatment plan. Nowadays, neuropsychological assessment usually consists of paper-and-pencil tests that are conducted in a quiet room where distractions are minimized. Although these tests are convenient to purely measure underlying cognitive functions, research has often reported a lack of ecological validity (Chaytor & Schmitter-Edgecombe, 2003; Dawson & Marcotte, 2017). Performances on paper-and-pencil tests do not translate easily to daily life functioning, which results in a poor understanding of the difficulties patients encounter in daily life (Donovan et al., 2008).

Ecologically valid assessment has evolved as an area of focus within clinical neuropsychology (Chaytor & Schmitter-Edgecombe, 2003). Several standardized tests has been developed with an improved ecological validity, such as the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996), the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985), and the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 1996)). However, even if most researchers agree that these tests seem similar to everyday tasks, participants remain well aware of the laboratory setting. For this reason, ecologically valid tests have been developed that are conducted in the real-world, such as the Multiple Errands Test (Shallice & Burgess, 1991) or the Executive Secretarial Task (Lamberts, Evans, & Spikman, 2010). A limitation, however, is the lack of a standardized and controlled setting, which results in an inconsistent degree of distractions within and between assessments.

Virtual Reality (VR) offers a novel possibility to assess cognitive functioning in simulated environments resembling daily life (Bohil, Alicea, & Biocca, 2011; Maggio, De Luca, et al., 2019; Parsey & Schmitter-Edgecombe, 2013; Parsons, 2011, 2015; Parsons, Carlew, Magtoto, & Stonecipher, 2017; Parsons, McPherson, & Interrante, 2014; Rizzo, Schultheis, Kerns, & Mateer, 2004; Schultheis, Himelstein, & Rizzo, 2002). VR allows the development of ecologically valid environments without losing control over stimulus presentation, while capturing precise and detailed performance measures due to a continuous data acquisition. In this study, we used two primary user interfaces, namely non-immersive VR by using a computer monitor (CM) and immersive VR by using a head-mounted display (HMD). CMs are considered the least interactive implementation of VR, but are often already accessible and

are therefore a low-cost implementation of VR. HMDs are considered the highest interactive implementation of VR and allow patients to be fully immersed and to interact naturally with the virtual environment. Although the use of VR in neuropsychological assessment has been promising, is it feasible to use in stroke patients? How do stroke patients experience non-immersive and immersive VR?

Feasibility studies are used to determine whether an intervention is appropriate for further testing, in other words, whether or not the ideas and findings can be shaped to be relevant (Bowen et al., 2009). The objective of this study was to determine the feasibility (as measured with objective parameters, such as completion rate), user-experience and preference (as measured with subjective parameters) of VR in stroke patients. We asked stroke patients to perform a VR-task in a virtual supermarket twice, one time by using a CM and one time by using a HMD. We investigated (1) potential differences in feasibility, user-experience, and a potential preference for one user interface over another between stroke patients and healthy controls; (2) potential differences in feasibility, user-experience, and preference between patients referred for *inpatient* rehabilitation care and patients referred for *outpatient* rehabilitation care; and (3) potential demographic and clinical characteristics that were related to patients' preference for one user interface over another.

Methods

Participants

In the Netherlands, stroke patients are referred for *inpatient* rehabilitation care when: (a) a safe discharge from hospital to home is not achievable within 5 days; (b) the patient is physically and cognitively capable to participate in therapy; (c) a multidisciplinary approach is essential to reach complex rehabilitation goals; and (d) discharge from inpatient rehabilitation to home is expected in view of the prognosis and availability of the caregivers within 3 months. Stroke patients are referred for *outpatient* rehabilitation care when: (a) a safe discharge from hospital to home is achievable; and (b) a multidisciplinary approach is essential to reach rehabilitation goals.

We recruited participants between June 2016 and July 2019. We recruited stroke patients who were referred for inpatient or outpatient rehabilitation care at *De Hoogstraat Rehabilitation Center*, and stroke patients who were referred for outpatient rehabilitation care at the *University Medical Center Utrecht*, the Netherlands. Outpatients referred for rehabilitation care are a very specific group of stroke patients that have a relative good outcome (so-called "walk and talk group"). Inclusion criteria for all patients were (1) clinically diagnosed with

stroke (confirmed by an MRI or CT scan); (2) aged ≥ 18 years; (3); physically and cognitively able to perform two VR-tasks as evaluated by the multidisciplinary team (clinicians who were actively engaged in the treatment, such as rehabilitation physicians, occupational therapists, neuropsychologists) and substantiated with objective measurements. When the opinion of the team was that motor or communication problems were so severe that patients could either not work with the joystick or controllers, or would not be able to understand task instructions or fill out the questionnaires, they would not be included in the study. The exclusion criteria were the diagnosis of (1) epilepsy (as the changing images could potentially trigger a seizure in patients with photosensitive epilepsy), and (2) severe visuo-spatial neglect based on a screening that was administered within the first two weeks of admission (care as usual). Patients who would largely ignore one side of space and were not able to compensate for this were excluded. Inpatients who met the inclusion criteria received more information about the study and participation was discussed. Outpatients were invited by an information letter handed out by a clinician or sent by post. Participation was discussed by phone. When patients were willing to participate, an appointment was scheduled that was appropriate given their individual rehabilitation schedule.

We recruited healthy controls among acquaintances and colleagues, and by using advertisements in newsletters in (elderly, sports) associations. We aimed to match age, sex, and level of education as best as possible. The inclusion criteria for healthy controls were: (1) no history of neurological and/or psychiatric disorders for which treatment was needed; and (2) aged ≥ 18 years. All participants gave written informed consent. The experiment was performed in accordance with the Declaration of Helsinki (The World Medical Association, 2008). The research protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht (METC protocol number 15-751/C).

Apparatus

A virtual supermarket was developed with the software Unity by Atoms2Bits for commercial purposes, and was adapted for research and potential clinical purposes in close collaboration with the *University Medical Centre Utrecht*, *De Hoogstraat Rehabilitation Centre*, and *Utrecht University*. It was designed to be used on a regular computer in combination with two user interfaces: a CM and a HMD. The virtual supermarket was modelled according to a regular Dutch supermarket and contained 18 shelves, eight cash registers, several product displays (e.g., bread, fruit, vegetables) and freezing compartments (Figure 7.1). Approximately 20,000 products were designed referring to real brands and packages from common products in Dutch supermarkets. The surface was 50 x 30 virtual meters. Participants navigated at a maximum speed of 0.5 meter per second.

Figure 7.1. Impression of the virtual supermarket used in this study (reprinted with permission of Atoms2Bits).

The CM was a 24 inch monitor with a resolution of 1920 x 1200 pixels. A wired controller was used to navigate (Xbox 360©). Participants were seated on an office chair in front of the CM, which was placed at approximately 90 cm from their eyes. Two types of HMDs were used in this study. Participants included in between June 2016 and February 2017 were tested with the Oculus Rift DK2© with a 100° field of view, a resolution of 960 x 1080 per eye, and a refresh rate of 75 Hz. A wired controller (Xbox 360©) was used to navigate. Participants included in between January 2018 and July 2019 were tested with the HTC Vive© with a 110° field of view, a resolution of 1080 x 1200 per eye, and a refresh rate of 90 Hz. The HTC Vive contained two controllers to navigate and two base stations with a tracking system for participants to navigate through real time movement in the virtual environment (maximum space of 3 x 3 meters). Since balance deficits are common in stroke patients (Geurts, De Haart, Van Nes, & Duysens, 2005), participants (healthy controls also) were seated on an office chair for safety reasons.

Procedure

Participants provided written informed consent before initiation of the experiment. Participants were asked to perform a VR-task twice, one time by using a CM and one time by using a HMD. To avoid a possible bias on the results due to learning or boredom, the order in which the conditions were administered was randomized: with half of the participants starting with the CM and the other half starting with the HMD (Figure 7.2). Participants received a practice trial to get familiar with the VR apparatus and environment (i.e., virtual

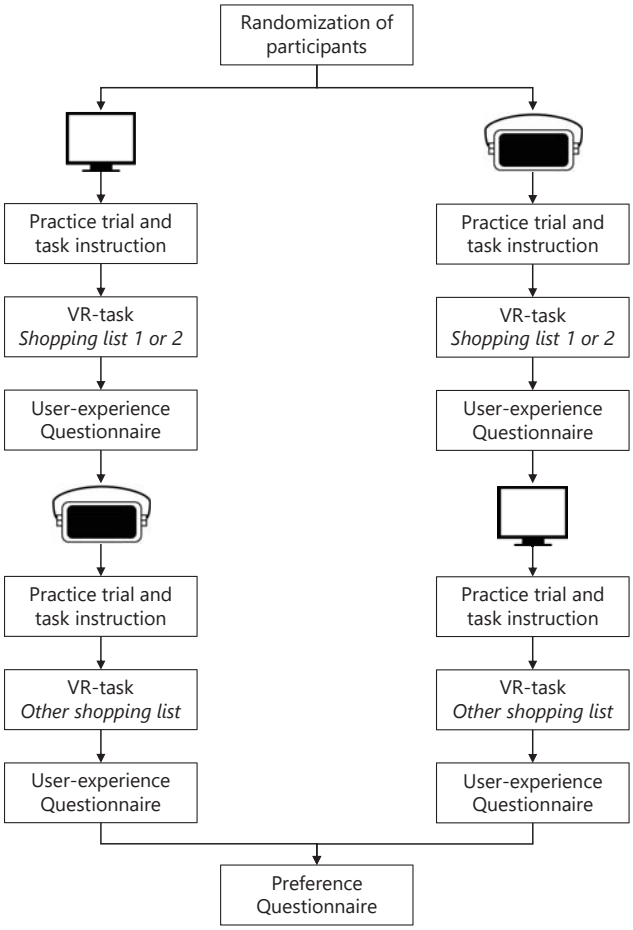

Figure 7.2. Procedure of the within subject design of this study.

supermarket with empty shelves to prevent a learning effect). After the practice trial, participants were instructed to (1) start the VR-task by passing through the entry gates, (2) find three products from a shopping list, and (3) pass the cash registers to finish. A grocery list was presented over three trials, and participants were asked to recall the products. There were two different shopping lists: (1) salt, matches, sprinkles; (2) hair wax, cookies, socks. The shopping lists were semi-randomised across conditions. Task duration was limited to 15 minutes per condition. After the VR-task, a questionnaire was administered to assess the user-experience. The procedure was then repeated with the other user interface. Finally, a questionnaire was administered to assess the preference for one of the two user interfaces. The total duration of the experiment was approximately one hour.

Outcome measures

Feasibility measures

To investigate the feasibility, we calculated the completion rate (i.e., number of participants who completed the VR-task, who aborted the VR-task, and who did not start the VR task because of negative side effects during the practice trial), the total time needed to complete the VR-task (in minutes), and the total number of products found that were presented on the shopping list (range 0–3).

Questionnaire regarding user-experience

We developed a questionnaire to measure the user-experience based on previous cross-media research (Lessiter, Freeman, Keogh, & Davidoff, 2001; Schuemie, Van der Straaten, Krijn, & Van der Mast, 2001; Weibel, Wissmath, Habegger, Steiner, & Groner, 2008). The questionnaire consisted of 15 items divided over five scales (three items per scale): (1) "engagement" defined as the feeling of involvement and enjoyment of the content; (2) "transportation" defined as the feeling of arriving in another world than the real world; (3) "flow" defined as a mental state in which a person is fully immersed in an activity with utmost concentration and distorted sense of time; (4) "presence" defined as the feeling of being physically present inside a virtual environment; (5) "negative effects" defined as adverse physiological reactions such as nausea. Response options were based on a 6-point Likert scale ranging from negative (--- [0]) to positive (+++ [5]). We summed the three items-scores belonging to a scale, resulting in a scale-score ranging from 0–15. An English translation of the questionnaire is presented in Appendix 7.1 (note that the results in this study are obtained with a Dutch version).

The face validity of the questionnaire was explored in an additional sample of 55 healthy controls (20% male, 89% high-educated, average age of 29.14 years [SD 9.78]). Those healthy controls did not participate in the main study. We asked the participants to cluster the items into five scales. A high percentage of participants clustered the right items into the scales engagement (86%), transportation (69%), and negative effects (96%), which indicated a valid face validity. A lower percentage of participants clustered the right items into the scales flow (40%) and presence (51%), which indicated a weaker face validity.

Questionnaire regarding preference

Participants were asked to indicate their preference for one of the two user interface in regard to five statements. The response options were: CM, HMD, or both. We quantified how many times a participant preferred the CM, HMD, or indicated to have no preference. An English translation of the questionnaire is presented in Appendix 7.2.

Demographic and clinical characteristics

We collected data on sex, age and level of education. Level of education was assessed using a Dutch classification system (Verhage, 1965), consisting of 7 levels ([1] less than primary education; [2] primary education; [3] primary education and less than 2 years of low-level secondary education; [4] low-level secondary education; [5] average-level secondary education; [6] high-level secondary education; [7] academic degree). These levels were converted into three categories for analysis: low (level 1–4), average (level 5), and high (level 6–7). We asked six questions about the participant's familiarity with (1) 2D games; (2) 3D games; (3) 3D games with "first persons view"; (4) keyboards/touchscreens; (5) controllers; and (6) VR. Response options were based on a 3-point Likert scale (– [0]; ± [1]; + [2]). The sum of the item scores was used as an indication of gaming experience, resulting in a score ranging from 0 (no gaming experience) to 12 (a great deal of gaming experience).

For all patients, we extracted time since stroke, stroke type (ischaemic, haemorrhage or subarachnoid haemorrhage) and lesion side (left, right or both) from the medical files. For inpatients, we extracted the scores on several clinical variables that were administered at admission as care as usual: communication skills as measured with the Stichting Afasie Nederland test (Deelman, Koning-Haanstra, Liebrand, & Van den Burg, 1981), independence during ADL as measured with the Barthel Index (Collin, Wade, Davies, & Horne, 1988), and motor strength of upper and lower extremities as measured with the Motricity Index (Collin & Wade, 1990). For outpatients, these clinical variables were not administered since these patients would have had a maximum score to support their clinical referral to outpatient rehabilitation care. Global cognitive functioning was measured with the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). This score was extracted from the medical files for inpatients and administered at the beginning of the test session for outpatients.

Statistical analyses

Demographic and clinical characteristics

We compared demographic and clinical characteristics between stroke patients and healthy controls by using non-parametric tests (Chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables).

Differences in feasibility, user-experience and preference between user interfaces (CM vs. HMD)

The development of VR HMDs is ongoing. Important differences may be seen between old generation HMDs and new generation HMDs (Kourtesis, Collina, Doumas, & MacPherson, 2019). Halfway through this study, we switched from the Oculus Rift DK2 to the more

sophisticated HTC Vive. To avoid a possible bias on the results, we first compared the feasibility, user-experience and preference between healthy controls who conducted the VR-task with the Oculus Rift DK2 (n = 33) and healthy controls who conducted the VR task with the HTC Vive (n = 33). We used non-parametric tests (Chi-square test for categorical variables and Mann-Whitney U test for continuous variables).

Furthermore, we compared the feasibility, user-experience and preference between the user interfaces (CM vs. HMD) and between patients and healthy controls. We used Chi-square tests (2 x 2), Fisher's exact tests (between-subject), and McNemar tests (within-subject) for categorical variables (i.e., completion rate, preference). We conducted a mixed analysis of variance (ANOVA) with "user interface" as a within-subject factor (CM vs. HMD) and "group" as a between-subject factor (stroke patients vs. healthy controls) for continuous variables (i.e., total time, total products, scale-scores). A Benjamini-Hochberg correction was applied to counteract the problem of multiple comparisons (Benjamini & Hochberg, 1995). False discovery rate was set at .1.

Potential effect of clinical referral on feasibility, user-experience and preference

We compared the feasibility, user-experience and a potential preference for one of the two user interface between patients who were referred for *inpatient* rehabilitation care (moderate to severe impaired patients) and patients who were referred for *outpatient* rehabilitation care (mild impaired patients). We used Chi-square tests, Fisher's exact tests, or McNemar tests for categorical variables and a mixed ANOVA for continuous variables.

Relations between demographic and clinical characteristics and patients' preference

Spearman correlations were computed between demographic (age, gaming experience) and clinical characteristics (MoCA score and time post-stroke onset) and preference for the CM, HMD, or both. An r of .1 was considered a small, .3 a moderate, and .5 a large relation (Field, 2009). The level of significance was set at p = .05.

Results

Demographic and clinical characteristics

From 249 stroke patients who were evaluated at the rehabilitation centre, 68 stroke patients were unable to participate as evaluated by clinicians (n = 52) or due to early discharge (n = 16). These numbers were not systematically recorded at the medical centre and no estimation can be given. A total of 181 patients were invited to participate, and 93 patients

did not respond or declined due to various reasons (e.g., no time/interest). In total, 88 stroke patients, from the rehabilitation and medical centre combined, were included in this study. In addition, 66 healthy controls were included. See Table 7.1 for the demographic and clinical characteristics. There were more men in the patient sample than in the healthy controls sample ($\chi^2(2) = 5.43$, p = .020). Healthy controls were younger ($U = 1847.50$, $z = -3.86$, $p < .001$), higher educated ($\chi^2(2) = 18.82$, $p < .001$), and had more gaming experience ($U = 1961.00$, $z = -3.47$, $p = .001$), when compared to stroke patients.

Table 7.1. Demographic characteristics (split for stroke patients and healthy controls) and clinical characteristics (split for stroke patients who were referred for inpatient and outpatient rehabilitation care)

Demographic characteristics	**Stroke patients** (*n* = 88)	*n*	**Healthy controls** (*n* = 66)	*n*
Sex (% male)*	61.4	88	42.4	66
Age in years (mean, SD)*	55.32 (13.72)	88	46.24 (15.60)	66
Level of education (%)*		88		66
Low	21.6		3.0	
Moderate	27.3		13.6	
High	51.1		83.3	
Gaming experience 0–12 (mean, SD)*	4.00 (2.80)	88	5.45 (2.72)	66
Clinical characteristics	**Inpatients** (*n* = 43)	*n*	**Outpatients** (*n* = 45)	*n*
Stroke type (%)		43		45
Ischemic	69.8		71.1	
Haemorrhage	25.6		4.4	
Subarachnoid haemorrhage	4.7		20	
Rare causes of stroke[1]	0		4.4	
Lesion side (%)		43		45
Left	46.5		28.9	
Right	41.2		40	
Bilateral	0		15.6	
Unknown	2.3		15.6	
Days post stroke (mean, range)	153.74 (245.69)	43	490.76 (634.68)	45
Montreal Cognitive Assessment 0–30 (mean, SD)	22.92 (4.84)	39	24.86 (3.97)	35
MoCA Score 26 or below (%)	62.8		44.4	
Stichting Afasie Nederland 1–7 (mean, SD)	6.08 (4.97)	36	Not applicable[2]	
Barthel Index 0–20 (mean, SD)	13.39 (5.37)	41	Not applicable[2]	
Motricity Index upper 0–100 (mean, SD)	62.59 (38.34)	39	Not applicable[2]	
Motricity Index lower 0–100 (mean, SD)	74.58 (31.95)	38	Not applicable[2]	

* Significantly different between stroke patients and healthy controls, *p*-value < .05. Note. [1] One patient diagnosed with cerebral venous sinus thrombosis and one patient with cerebral fat embolism, which are less common causes of stroke. [2] These clinical variables were not administered since patients would have had a maximum score to support the clinical referral for outpatient rehabilitation care.

Differences in feasibility, user-experience and preference between user interfaces (CM vs. HMD)

Healthy controls who were tested with the Oculus Rift DK2 completed the VR-task less often ($\chi^2(2) = 8.41$, $p < .001$), reported less transportation ($U = 358.50$, $z = -2.24$, $p = .025$), less flow ($U = 379.00$, $z = -1.97$, $p = .049$), less presence ($U = 330.50$, $z = -2.46$, $p = .014$), more negative effects ($U = 313.50$, $z = -2.83$, $p = .005$), and had a distinct preference for the CM ($\chi^2(2) = 42.62$, $p < .001$), when compared to healthy controls who were tested with the HTC Vive. To avoid a possible bias of the type of HMD on the results, we only used the data of patients ($n = 74$) and healthy controls ($n = 33$) who were tested with the more sophisticated HTC Vive in further analyses. The HTC Vive offered a better quality and further VR HMD development would only make the devices better suited.

Stroke patients did not abort the VR-task more often than healthy controls with the CM (Fisher's exact, $p = .592$) nor with the HMD (Fisher's exact. $p = .732$). Stroke patients did complete the VR-task more often with the CM than with the HMD (McNemar test, $p = .039$). Based on a mixed ANOVA, we found a main effect of group, where stroke patients needed more time ($F(1, 88) = 18.97$, $p < .001$) and found less products ($F(1, 89) = 10.13$, $p = .002$), compared to healthy controls (Table 7.2). We found a main effect of user interface, where both patients and healthy controls reported an enhanced feeling of engagement ($F(1, 96) = 21.99$, $p < .001$), transportation ($F(1, 98) = 132.10$, $p < .001$), flow ($F(1, 98) = 29.60$, $p < .001$), and presence ($F(1, 94) = 109.75$, $p < .001$), but more negative effects ($F(1, 98) = 47.92$, $p < .001$) when tested with the HMD, compared to the CM. There was no significant difference in preference for one user interface between stroke patients and healthy controls ($\chi^2(2) = 4.88$, $p = .088$), with the majority reporting to have no preference (Figure 7.3).

Table 7.2. Feasibility in stroke patients and healthy controls, split for user interface (CM vs. HMD)

	Stroke patients ($n = 74$)		**Healthy controls** ($n = 33$)	
	Computer monitor	Head-mounted display	Computer monitor	Head-mounted display
Completion rate (%)	93.2	83.8	100	90.9
Aborted during VR-task (%)	4.1	10.8	0	6.1
Aborted after practice trial (%)	2.7	5.4	0	3.0
Total time to complete VR-task[1] (minutes)	10.46 (4.56)	10.15 (4.29)	7.47 (3.94)	7.31 (3.50)
Total number of found products[1] (0–3)	2.49 (.77)	2.43 (.96)	2.93 (.25)	2.87 (.43)

Note. [1] Participants who did not start (6 patients; 1 healthy control) or complete (7 patients; 2 healthy controls) one of the two conditions were excluded from these analyses (included: 61 patients; 30 healthy controls).

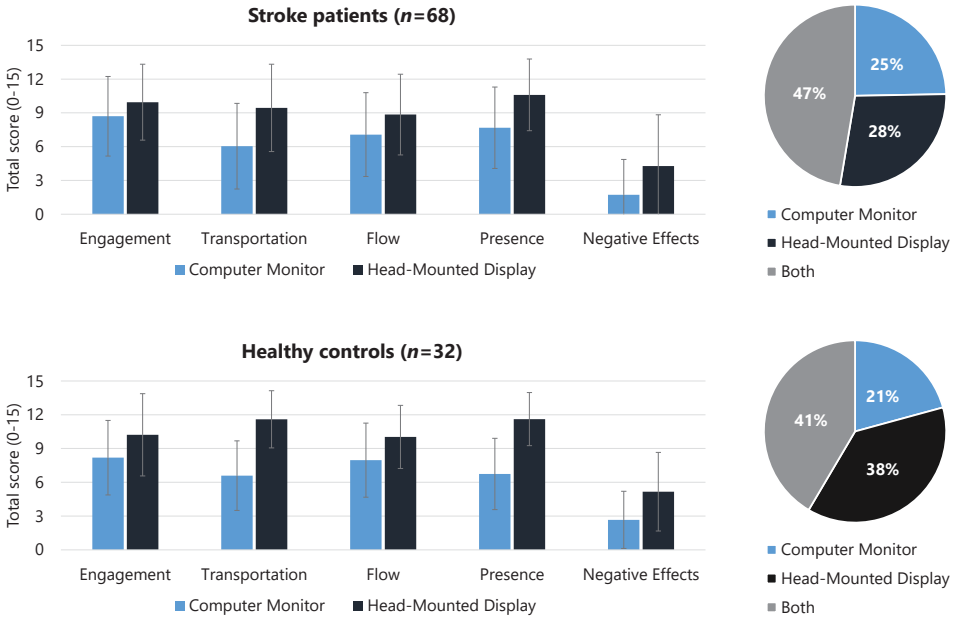

Figure 7.3. The user-experience of both user interface (CM vs. HMD) and the preference (for CM, HMD, or both) is depicted, split for stroke patients and healthy controls. Note that patients (n = 6) and healthy controls (n = 1) who did not start one of the two conditions were excluded from these analyses (included patients n = 68; healthy controls n = 32). Number of participants varies per variable since data was missing on one question within a scale for 6 participants.

Potential effect of clinical referral on feasibility, user-experience and preference

Patients who were referred for *inpatient* rehabilitation care did not abort the VR-task more often than patients who were referred for *outpatient* rehabilitation care with the CM (Fisher's exact = 1.33, p = .632), nor with the HMD (Fisher's exact = 612, p = .797). Outpatients reported significantly more negative effects compared to inpatients (F (1, 66) = 7.22, p = .009). We only found an interaction effect (group x user-interface) on the feeling of engagement (F (1, 59) = 8.66, p = .005). Outpatients, in comparison to inpatients, reported a significant improved feeling of engagement when conducting the VR-task with the HMD, compared to the CM. There was no significant difference in preference for one user interface between the patient groups (χ^2(2) = 1.41, p = .494), with the majority reporting to have no preference (Table 7.3).

Table 7.3. Feasibility, user-experience and preference, split for stroke patients who were referred for inpatient rehabilitation care and patients who were referred for outpatient rehabilitation care

	Inpatients (*n* = 43)		**Outpatients** (*n* = 31)	
	Computer monitor	Head-mounted display	Computer monitor	Head-mounted display
Feasibility				
Completion rate (%)	90.7	86	96.8	80.6
Aborted during VR-task (%)	4.7	9.3	3.2	12.9
Aborted after practice trial (%)	4.7	4.7	0	6.5
Completion time VR-task[1] (minutes)	11.14 (4.34)	10.20 (4.63)	9.44 (4.78)	10.07 (3.82)
Total number of found products[1] (0–3)	2.56 (.67)	2.31 (1.06)	2.40 (.87)	2.60 (.76)
User-experience[2]				
Engagement (0–15)	9.55 (3.24)	9.87 (3.40)	7.54 (3.63)	10.07 (3.39)
Transportation (0–15)	5.87 (3.89)	9.56 (3.82)	6.28 (3.75)	9.28 (4.02)
Flow (0–15)	7.64 (3.88)	9.41 (2.91)	6.31 (3.40)	8.10 (4.10)
Presence (0–15)	8.00 (3.58)	10.59 (3.73)	7.19 (3.69)	10.62 (2.16)
Negative effects (0–15)	.87 (1.87)	3.28 (4.44)	2.86 (4.06)	5.62 (4.42)
Preference[2]	**Inpatients** (*n* = 43)		**Outpatients** (*n* = 31)	
Computer monitor	22%		28%	
Head-mounted display	30%		25%	
Both	48%		47%	

Note. [1] Participants who did not start (4 inpatients; 2 outpatients) or completed (3 inpatients; 4 outpatients) one of the two condition were excluded from these analyses (included: 36 inpatients; 25 outpatients). [2] Participtants who did not start one of the two conditions were excluded from these analyses (included: 39 inpatients; 29 outpatients). Number of participants varies per variable since data was missing on one question within a scale for 5 participants.

Relations between demographic and clinical characteristics and patients' preference

Age and preference for the HMD were negatively related among stroke patients. Patients who were younger tended to prefer the HMD over the CM more often. There was no relation between preference and gaming experience, general cognitive functioning and days post stroke onset (Table 7.4).

Table 7.4. Relation between demographic and clinical characteristics and preference for one user interface in stroke patients (*n* = 68)

	Age	**Gaming experience**	**MoCA score**	**Days post-stroke**
Preference for head-mounted display	-.25 (*p* = .043)*	.18 (*p* = .135)	.09 (*p* = .474)	-.13 (*p* = .279)
Preference for computer monitor	-.01 (*p* = .928)	-.09 (*p* = .489)	.06 (*p* = .629)	.13 (*p* = .304)
No preference	.19 (*p* = .116)	-.076 (*p* = .54)	-.048 (*p* = .707)	.06 (*p* = .650)

* $p < .05$. Note. MoCA scores were extracted from medical files for inpatients and administered at the beginning of the test session for outpatients. Results should be interpreted with caution.

Discussion

In this study, stroke patients performed a VR-task in a *virtual supermarket* twice, one time by using a CM and once time by using a HMD. We investigated (1) potential differences in feasibility, user-experience, and a potential preference for one user interface over another between stroke patients and healthy controls; (2) potential differences in feasibility, user-experience, and preference between patients referred for *inpatient* rehabilitation care and patients referred for *outpatient* rehabilitation care; and (3) potential demographic and clinical characteristics that were related to patients' preference for one user interface over another. A high percentage of patients completed the VR-task when tested with a CM (93%) and a HMD (84%). This suggests that it is feasible to use both non-immersive and immersive VR user interfaces (CM and HMD) in stroke patients. Patients and healthy controls reported an enhanced feeling of engagement, transportation, flow, and presence when tested with the HMD, when compared to the CM. Hence, the use of a HMD evokes an enhanced user-experience, which is expected to lead to a more natural behaviour and interaction with the virtual environment (Parsons, 2015). However, more adverse physiological reactions were reported by both stroke patients and healthy controls when tested with a HMD, when compared to a CM. Negative effects are expected to decrease with further VR HMD development (Kourtesis et al., 2019), which was also shown in this study where healthy controls experienced more negative effects when tested with the older Oculus Rift DK2 compared to the more sophisticated HTC Vive. Current best practice guides for VR development focus on alleviating negative effects by using several approaches to reduce sensory mismatch, such as display factors (e.g., higher refresh rates) and intuitiveness of interaction and navigation (Kourtesis et al., 2019; Kourtesis, Korre, Collina, Doumas, & MacPherson, 2020; Oculus, 2017; Weech, Kenny, & Barnett-Cowan, 2019). Furthermore, negative effects decrease over repeated exposures, which emphasises the importance of practice trials to help a user become more familiar with a particular device (Germine, Reinecke, & Chaytor, 2019; Kennedy, Stannney, & Dunlap, 2000). Importantly, stroke patients reported no preference for one user interface (CM vs. HMD), which increases the usability of VR in clinical practice as patients are willing to work with both user interfaces with their own set of strengths and limitations. This allows for a tailor-made application, dependent of the aim of the assessment and the willingness of a patient. The use of a HMD seems preferable in neuropsychological assessment since it induces more natural behaviour, but a CM remains a valid alternative when a HMD is not accessible or not feasible with a particular patient.

We did not find an effect of clinical referral to *inpatient* or *outpatient* rehabilitation care on the feasibility, user-experience and preference, which indicates that VR (when using a CM or HMD) is feasible in patients who are more severely injured by stroke. Indeed, general

cognitive functioning did not affect the preference for one user interface, nor did the time post stroke onset. We only found a small negative relation between age and preference for the HMD, indicating that younger patients tended to prefer a HMD over a CM more often. Gaming experience did not affect the preference in our sample. One should be cautious however, as only limited research on this topic has been performed in stroke patients and opposite effects have also been reported in healthy controls (Weech et al., 2019). A next step on this topic, would be the investigation whether gaming experience would affect cognitive performance in a virtual environment. Previous research shows that individuals with more computer experience tend to demonstrate a better cognitive performance on computer-based assessment, than individuals with less computer experience (Iverson, Brooks, Ashton, Johnson, & Gualtieri, 2009; Tun & Lachman, 2010). This might also be the case with VR-based assessments (Iverson et al., 2009; Tun & Lachman, 2010). This would mainly mean that we might have to facilitate longer practice trials for patients with less gaming experience, to help them get more familiar with the devices and virtual environment.

Strengths and limitations

A strength of this study was the inclusion of a large number of stroke patients (n = 88) and the recruitment in both a rehabilitation centre and medical centre, which increases the representativeness of our sample, at least for the way rehabilitation care is organised in the Netherlands. The sample of stroke patients in this study encompasses a wide range of severity of stroke and severity of *consequences* of stroke. Furthermore, research emphasizes the importance of including patients in the evaluation of new medical technological devices (Lee, 2019), so incorporating the user-experience and preference of stroke patients provides useful insights into the use of VR in clinical practice. An unknown factor, however, is the feasibility, user-experience and preference of the more severely hampered stroke patients. Clinicians evaluated whether participation would be made possible, and we excluded patients with interfering impairments (e.g., severe motor problems hindering the use of a controller, severe communication problems preventing them to understand the instruction, severe fatigue). The feasibility of VR in severely injured patients remains therefore unknown. This may be considered as a limitation, as using VR could make the whole testing experience less threatening and more enjoyable, which in turn could motivate patients to undergo assessment more often and monitor their cognitive functioning more closely (Zygouris & Tsolaki, 2015).

A limitation that should be considered, is that a part of the stroke patients and healthy controls was excluded from further analyses, due to significant differences in user-experience when comparing the Oculus Rift DK2 and the HTC Vive. This resulted in smaller samples of especially healthy controls for the subsequent analyses (stroke patients from n = 88 to

n = 74; healthy controls from n = 66 to n = 33). For the feasibility, user-experience and preference of stroke patients this most likely did not have a large effect, yet for comparisons of these results with those of the healthy controls, we need to be cautious. Another potential limitation is the difference in demographic characteristics and gaming experience of the healthy controls and patients. Even though we tried to match age, sex, and level of education of both groups, the healthy controls were younger and higher educated. Also, there were more men among stroke patients. For the aims on feasibility and preference among the stroke patients, this does not have large impact, but when comparing the outcomes of the stroke patients to those of the healthy controls, we cannot be sure that the current results (i.e., feasibility, user-experience and preference) would be comparable with an older and lower educated sample of healthy controls. For the feasibility, user-experience and preference of stroke patients, this does not change the conclusion.

We used questionnaires as subjective parameters to assess user-experience and preference. The questionnaire regarding user-experience has given important insights into the five scales (engagement, transportation, flow, presence, negative effects). With regard to the CM condition, few negative effects were reported, namely nausea (7% of patients; 12% of healthy controls), feeling warm (13% of patients, 19% of healthy controls) and having a headache (11% of patients; 5% of healthy controls). With regard to the HMD condition, more negative effects were reported, namely nausea (32% of patients; 54% of healthy controls), feeling warm (47% of patients, 65% of healthy controls) and having a headache (20% of patients; 14% of healthy controls). However, one might argue that it was not elaborated enough. For example, "dizziness" was not part of the scale "negative effects". Certain patients (e.g., patients with cerebellar and/or midbrain stroke) might experience dizziness in daily life situation, and thus also while performing a VR-task. As "dizziness" has been a commonly reported effect of VR (Szpak, Michalski, Saredakis, & Loetscher, 2019), it seems crucial to incorporate "dizziness" as item in future studies. Furthermore, the preference questionnaire did not have the response option "none/neither", so based on the questionnaire, we would not be able to know whether there were patients that would not like to use VR at all. Informal feedback, however, suggests that patients do see the potential of such technology, as virtual environments resemble real-life environments and replicate the challenges found in daily life situations. This feedback is very valuable as it stresses the relevance of VR-tasks in neuropsychological assessment.

Future research

VR offers the opportunity to gain valuable information which cannot be obtained through paper-and-pencil tests, such as wayfinding features (e.g., crossing one's own pathway, location and duration stops), eye movement features (e.g., fixation duration, number of re-fixations,

pupillometry), and time-based measures (e.g., reaction time, fluctuations in pace) (Lutz et al., 2017; Parsey & Schmitter-Edgecombe, 2013). A first step should be the development of outcome measures, on which patients with impaired cognitive functions perform significantly different than cognitively healthy controls. For instance, based on the relatively simple outcome measures in this study, we found that stroke patients needed more time and found less products, when compared to healthy controls. Numerous studies describe VR-tasks in different populations and report significant differences in performance between patients and healthy controls. For instance, a VR office and meeting room is used to test patients with frontal lobe lesions on multitasking abilities by evaluating the quality of the performance on different tasks (failure, partial or satisfactory completion) (Denmark et al., 2019), and a VR shopping task is used to test patients with traumatic brain injury on prospective memory by evaluating event-based measures (press button when sale-announcement is heard) and time-based measures (send text message at three different time points) (Canty et al., 2014). A next important step is the development of outcome measures to accurately discriminate patients from healthy controls. For instance, a virtual supermarket task showed a correct classification of 87% when discriminating patients with mild cognitive impairment from healthy controls with outcome measures, such as test duration and correctly bought products (Zygouris et al., 2015). A combination of outcome measures, may be used to identify distinct pattern of scores discriminating patients and healthy controls more accurately. In a large sample, data-driven machine learning analyses might reveal which behavioural patterns occur from the data. Data-driven analyses may enable a shift towards developing more sophisticated models of behaviour to further improve the sensitivity of neuropsychological assessment by using VR-tasks. Finally, a next step would be the validation and the reliability of the VR-task, followed with the derivation of normative data to help clinicians interpret the complementing information (Iriarte et al., 2012).

Finally, previous research has reported promising results in using VR in cognitive rehabilitation (Larson, Feigon, Gagliardo, & Dvorkin, 2014; Laver, George, Thomas, Deutsch, & Crotty, 2015; Maggio, Latella, et al., 2019; Moreno et al., 2019; Rizzo et al., 2004; T. Rose, Nam, & Chen, 2018; Shin & Kim, 2015). The use of VR in cognitive rehabilitation may have important benefits, such as the opportunity to train skills and compensation strategies in a safe environment while interacting with people and/or objects (F. D. Rose, Brooks, & Rizzo, 2005).

Conclusions

In this study, we found that the use of both non-immersive and immersive VR user interfaces (CM and HMD) is feasible in stroke patients, irrespective of clinical referral for inpatient

or outpatient rehabilitation care. Patients reported an enhanced feeling of engagement, transportation, flow, and presence, but more negative effects when tested with a HMD, when compared to a CM. Negative effects are likely to decrease with more sophisticated HMD, which is a lead focus in best practice guides for VR development. The majority of stroke patients had no preference for one user interface, yet younger patients tended to prefer HMDs more often. Future research should focus on novel outcome measures, the validation and reliability, and the development of normative data.

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Appendix 7.1. Questionnaires regarding user-experience translated in English. Note that the results of this study were obtained with the original Dutch version.

Through this questionnaire, we want to ask about your experience with the virtual environment. Please take your time and choose the most suitable answer for each question.	– – –	– –	–	+	+ +	+ + +
1. I was hardly aware of the real world.						
2. I had the feeling to be transported into another world.						
3. I only paid attention to the virtual environment and less to second thoughts.						
4. I wanted to explore the virtual environment.						
5. I felt nauseous.						
6. I was part of the virtual environment.						
7. I felt present in the virtual environment.						
8. I felt warm.						
9. I was curious about the virtual environment.						
10. At the end of the task, I felt I was coming back from another world.						
11. I had a headache.						
12. I forgot the time.						
13. The virtual environment drew my attention.						
14. I felt immersed in the virtual environment.						
15. At the start of the task, I felt like stepping into another world.						

Note. The questionnaire consisted of five scales: engagement (items 4, 9, 13); transportation (items 2, 10, 15); flow (items 1, 3, 12); presence (items 6, 7, 14); negative effects (items 5, 8, 11).

Appendix 7.2. Questionnaires regarding preference for one of the two user interfaces translated in English. Note that the results of this study were obtained with the original Dutch version.

Through this questionnaire, we want to ask you which user interface you prefer. Please take your time and choose the most suitable answer for each question.	Head-mounted display	Computer monitor	Both
1. I was motivated to perform the VR-task.			
2. I enjoyed the VR-task.			
3. I would like to do the VR-task again.			
4. I would like to do the VR-task at home.			
5. I would like to do the VR-task regularly.			

In April 2016, me and my father were driving our car on a country road. My father had to brake to turn into a small road and the driver behind us did not see us slow down. He hit us from behind, which caused us to hit a lamp post. An ambulance took us to the hospital. My back and my head hurt, but they mainly paid attention to my back. My back was bruised and I was discharged from the hospital after an hour. Even in the hospital they did not pay attention to my head. At home, I took some rest for two weeks and my back recovered almost completely. At that time I was studying to become a speech therapist. When I started school again, I noticed that I was not able to keep up. I was forgetful and had trouble concentrating. It took me a while before I asked for help. In 2017, my general practitioner referred me for rehabilitation care. They conducted a neuropsychological assessment, which costed me a lot of energy. I did relatively well, but they found some shortcomings regarding my memory. I started occupational therapy to learn strategies to improve my functioning. It was challenging, as I already came up with several solutions myself. Acquired brain injury is still a big misunderstood thing, as people do not notice anything about a person with brain injury. I think that research is important to get more insight into what is going on in our brain.

Chapter 8

Novel insights into the rehabilitation of memory post acquired brain injury: A systematic review

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Abstract

Objective: Acquired Brain Injury (ABI) frequently results in memory impairment causing significant disabilities in daily life and is therefore a critical target for cognitive rehabilitation. Current understanding of brain plasticity has led to novel insights into *remediation*-oriented approaches for the rehabilitation of memory impairment. We describe 3 of these approaches that have emerged in the last decade: Virtual Reality (VR) training, Computer-Based Cognitive Retraining (CBCR) and Non-Invasive Brain Stimulation (NBS) and evaluate its effectiveness.

Methods: A systematic literature search was completed in regard to studies evaluating interventions aiming to improve the memory function after ABI. Information concerning study content and reported effectiveness were extracted. Quality of the studies and methods were evaluated.

Results: A total of 786 studies were identified, 15 studies met the inclusion criteria. Three of those studies represent the VR-based training, 7 studies represent CBCR and 5 studies represent NBS. All 3 studies found a significant improvement of the memory function after VR-based training, however these studies are considered preliminary. All 7 studies have shown that CBCR can be effective in improving memory function in patients suffering from ABI. Four studies of the 5 did not find significant improvement of the memory function after the use of NBS in ABI patients.

Conclusion: On the basis of this review, CBCR is considered the most promising novel approach of the last decade because of the positive results in improving memory function post ABI. The number of studies representing VR were limited and the methodological quality low, therefore the results should be considered preliminary. The studies representing NBS did not detect evidence for the use of NBS in improving memory function.

Introduction

Memory impairment is a common consequence of Acquired Brain Injury (ABI) which causes significant disabilities and is therefore a critical target for cognitive rehabilitation (Hall, Hall, & Chapman, 2005; Yip & Man, 2013). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively injure the brain. The majority of ABI is caused by Traumatic Brain Injury (TBI) and haemorrhagic or ischemic stroke (Holmqvist, Kamwendo, & Ivarsson, 2009). Within the *TBI* population, the percentage of people suffering from some form of memory impairment ranges from 20% to 79%, depending on the severity of the (closed) head trauma, the time of measurement, and the instruments used. Even after 1 year, 4% to 25% of TBI patients show some form of memory impairment (Cappa et al., 2011). The prevalence of memory dysfunction *post-stroke* varies from 23% to 55% in the first 3 months, which declines 1 year post-stroke to a percentage between 11% and 31% (Aben et al., 2013; das Nair & Lincoln, 2007; Snaphaan & De Leeuw, 2007). Memory impairment can hamper independence in activities of daily living, as well as return to work, social participation and the overall quality of life (Fish, Manly, Emslie, Evans, & Wilson, 2008). For this reason and the high prevalence of memory impairment after ABI, there is an urgent need for effective cognitive rehabilitation.

There are 2 main approaches within memory rehabilitation. First, *remediation* by restoration or retraining of the function; and second, *compensation* referring to any compensatory strategies, environmental modifications, and intact cognitive functions to overcome limitations in daily life. *Remediation* of the function is primarily due to some degree of spontaneous recovery (Cramer, 2008). The understanding of spontaneous recovery has been accompanied by the development of a wide range of therapeutic approaches that target brain repair by restoration. These can be referred to as *remediation*-oriented therapies, the aim of which is not to salvage threatened tissue but to promote restoration of function. Retraining of the function is based on the assumption that impaired memory will respond to mental exercise in the same manner as muscles respond to physical exercise and that repetitive training in one memory task may generalize to improved performance on other tasks within the same memory system (Brooks & Rose, 2003). The hypothesis is that the capacity of the function improves if the training is successful and does not depend on context or learning abilities (Björkdahl, Åkerlund, Svensson, & Esbjörnsson, 2013). Unfortunately, until recently there was little empirical evidence to indicate that these techniques are of much benefit to patients as any improvement on specific tasks practiced have not been found to generalize to other similar tasks (Brooks & Rose, 2003; Rees, Marshall, Hartridge, Mackie, & Weiser, 2007).

On the contrary, Rees et al. (2007) found strong evidence for the use of *compensation* for lost or deficient memory function. Therefore, most memory rehabilitation interventions focus on alleviating memory problems on functional level (i.e., level of activity in daily life), without necessarily improving the underlying memory function (Rees et al., 2007). Current memory treatment programs have focused on teaching patients the use of internal strategies (e.g., repeating, counting, face-name associations, categorizing, mental visualization or rhyming mnemonics) and/or external strategies (e.g., diaries, notebooks, to-do lists, electronic organizers, pagers) to help remember and recall information (Fish et al., 2008). In an updated review of evidence-based rehabilitation, Cicerone et al., (2011) recommended training in the use of external compensation strategies (including assistive technology) with direct application to daily activities as a practice guideline for individuals with moderate to severe memory impairment after TBI or stroke.

In brief, there has been little research showing that memory can be improved through *remediation*-oriented therapies and hence *compensation* approaches are the treatment choice. However, with the recently maturing fields in cognitive neurosciences, neuroplasticity shows greater promises then previously assumed and has yielded new interdisciplinary approaches (Miniussi et al., 2008). Neuroplasticity is the ability of the brain to create, strengthen, and modify neurological connections. It occurs at many levels from molecules to cortical reorganization. *Remediation*-oriented rehabilitation, based on neuroplasticity, can not only modify neural connections, but can also lead to functional relearning (Kimberley, Samargia, Moore, Shakya, & Lang, 2010). This allows brain injured patients to relearn new knowledge and establish new skills (Li, Robertson, Ramos, & Gella, 2013).

The current understanding of brain plasticity has led to novel insights in the rehabilitation of memory deficits. However, an overview of these insights is missing. The aim of this systematic review is to describe novel memory rehabilitation interventions based on *remediation*-oriented techniques post ABI and evaluate its effectiveness. This review will not include studies evaluating pharmacological intervention as pharmacological therapies were considered not suitable for targeting only the memory function without affecting other cognitive functions. We will describe 3 non-pharmacological approaches aiming at restoring the memory function that have emerged in the last decade: Virtual Reality (VR) training, Computer-Based Cognitive Retraining (CBCR) and Non-Invasive Brain Stimulation (NBS).

Virtual Reality

Virtual environments represent many real-life situations and are programmed to record accurate measurements of the individual's performance assessing the underlying function

(Brooks & Rose, 2003). VR is an interactive computer technology which creates the illusion of being in an artificial world. An fMRI study indicated that virtual-based environments are able to activate the related brain parts as in the real environment (You et al., 2005). The transfer of learned skills from VR training to real-life situations has been reported, which shows a high ecological validity (Brooks & Rose, 2003). VR is often used to obtain a realistic and controlled assessment of memory impairment in a rehabilitation setting (Brooks, Rose, Potter, Jayawardena, & Morling, 2004). However, the use of VR in rehabilitation is not only useful as an assessment tool, but also as the potential to offer a training method restoring the memory function.

Computer-Based Cognitive Retraining

CBCR, based on intensive repetition, aims at improving cognitive skills needed to successfully receive sensory input, process information, and react without any use of external aids (Li et al., 2013). CBCR is available to the patient at home and offers stimulating tailored programs that can be modified to the individual's progress. Ample evidence is found suggesting CBCR is effective in the recovery of working memory (WM) (Olesen, Westerberg, & Klingberg, 2004). Studies investigating CBCR in healthy participants showed that training can increase WM capacity and that training-induced changes in brain activity occur (Olesen et al., 2004; Westerberg et al., 2007). Additionally, training effects can be generalized to non-trained WM tasks, and to tests on attention, reasoning, and problem solving. Transfer of the training effects to non-trained WM tasks is consistent with the notion of training-induced plasticity in a common neural network for WM. The observed training effects suggest that WM training could be used as a *remediation* intervention for individuals for whom low WM capacity is a limiting factor in everyday life (Klingberg, 2010).

Non-invasive Brain Stimulation

Different neurophysiologic strategies to increase the activity of the injured brain area have been proposed mainly using Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). TMS is based on the principle of electromagnetic induction and causes depolarization and hyperpolarization in the neurons. Lower frequencies of repetitive TMS is called repetitive Transcranial Magnetic Stimulation (rTMS), which is a train of TMS pulses delivered at constant intervals on the same intensity (low-frequency 1–4 Hz, high-frequency 5–10 Hz). rTMS presents the opportunity to interact even more effectively with cortical activity (Miniussi et al., 2008). tDCS consists of placing 2 rubber electrodes on the scalp in order to allow a weak direct current to flow from anode to cathode. The electrical stimulus that reaches the brain is of enough intensity to modify the

level of spontaneous neuronal excitability and activity by changing the resting membrane potential. tDCS is easier to apply and less expensive then TMS (Johansson, 2011). Several studies emphasize the fact that interacting with cortical activity by cortical stimulation can positively affect cognitive performance and improve the rehabilitation potential (Miniussi et al., 2008). The therapeutic strategy of NBS consists of modulating an adaptive organization, allowing for the formation of functionally appropriate neural connections and enhancing behavioural recovery (Villamar, Santos Portilla, Fregni, & Zafonte, 2012). Preliminary evidence suggests that NBS may play a role in treating unilateral neglect (Lim, Kang, & Paik, 2010; Nyffeler, Cazzoli, Hess, & Müri, 2009) and aphasia (Naeser et al., 2005; Szaflarski et al., 2011).

To summarize, the aim of this review is to provide an overview of the studies characterizing the most discussed memory *remediation*-oriented techniques developed in the last decade; VR, CBCR, and NBS.

Methods

Search method and article selection

A systematic literature search was performed using PubMed and Web of Science for studies published between January 2004 and August 2014 using the terms *Acquired Brain Injury*, *(Traumatic) Brain Injury* or *Stroke* in combination with *Virtual Reality*, *Computer-Based Cognitive Retraining*, *Computerized Training*, *Non-Invasive Brain Stimulation*, *Transcranial Magnetic Stimulation*, *repetitive Transcranial Magnetic Stimulation* or *transcranial Direct Current Stimulation* as well as *Memory*. The search in PubMed was limited in the following features: publication date (published in the last 10 years), species (human), adults (≥ 19 years of age), and language (English). Likewise, the search in Web of Science was limited in the following features: language (English) and time span (2004 to 2014).

Intervention studies for improving memory function after ABI were selected when they met the following inclusion criteria: (1) individuals experiencing memory deficits resulting from ABI as confirmed by neurological examination; (2) ≥ 18 years of age; (3) studies using specific measurements of memory functioning consisting of objective measures of memory function using standardized memory tests or batteries; and (4) had a study design with at least a pre and post intervention measurement. Memory treatment was considered any cognitive intervention attempting to improve memory, with neuropsychological tests as outcome measures. Studies published in languages other than English were excluded.

The first author (L.A.S.) conducted the search and screened the titles and abstracts, followed by an exclusion of duplicates. From screen-positive abstracts, full-text articles were collected when available and evaluated. In case the first author had doubt about inclusion of an article, the other authors were consulted. Articles meeting the aforesaid criteria were included in the final selection. The final selection was checked by the other authors as well.

Data extraction

After the final selection, data extraction was performed by the first author (L.A.S.) and was based on data extraction methods from similar reviews (Schrijnemaekers, Smeets, Ponds, Van Heugten, & Rasquin, 2014). In case of doubt about which data to be extracted, the other authors were consulted. The following *study characteristics* were extracted from the articles: authors, design of the study, number of patients, outcome measures, *p*-value, and timing of measurements. The following *intervention characteristics* were extracted from the articles: aim of intervention, type of intervention, duration and intensity. The following *patient characteristics* were extracted from the articles: diagnostic criteria and severity, age, and time after onset. Results were considered to be positive when statistically significant at a *p*-value of $< .05$ level.

Quality assessment

Two authors (L.A.S. and T.C.W.N.) independently appraised the characteristics and the quality of the selected studies. The methodological quality was evaluated based on the following elements: 1) randomization of intervention or different condition, 2) comparison of an experimental group and a control group that received either an alternative form of treatment or no memory intervention, 3) blinding of participants, 4) blinding of researchers, 5) reporting completeness of follow-up (Tijssen & Assendelft, 2003). We added 3 relevant elements to evaluate the methodological quality: 6) group size (≥ 10 per group), 7) reporting effect size, and 8) reporting time post-ABI. We consider it important to report the time between the injury onset and the start of the intervention, to facilitate a comparison of the effect and to gain insights into the phase in which the patients were at time of the intervention (sub-acute phase vs. chronic phase). This 8-point checklist yielded a total score between 0 to 8. Each study was given a total score and consequently divided into high (total scores ≥ 6), moderate (≥ 3 and ≤ 6), and low (≤ 3) quality studies (Schrijnemaekers et al., 2014). Additionally, a distinction was made between effectiveness studies and feasibility studies for the interpretation of the results of each study.

Results

The initial search identified 786 articles that were evaluated according to the inclusion criteria. Ultimately, 15 articles met the full inclusion criteria and were used for this review (see Figure 8.1). Of these 15 studies, 3 studies represented VR-based training, 7 studies represented CBCR, and 5 studies represented NBS. The specifics of the selected studies are presented in Tables 8.1–8.3 for results on VR, CBCR, and NBS respectively. After briefly describing these studies, we present the findings of the methodological quality based on the elements mentioned above (for total overview see Table 8.4). There was a 95% agreement between the 2 authors (L.A.S. and T.C.W.N.) regarding the quality assessment.

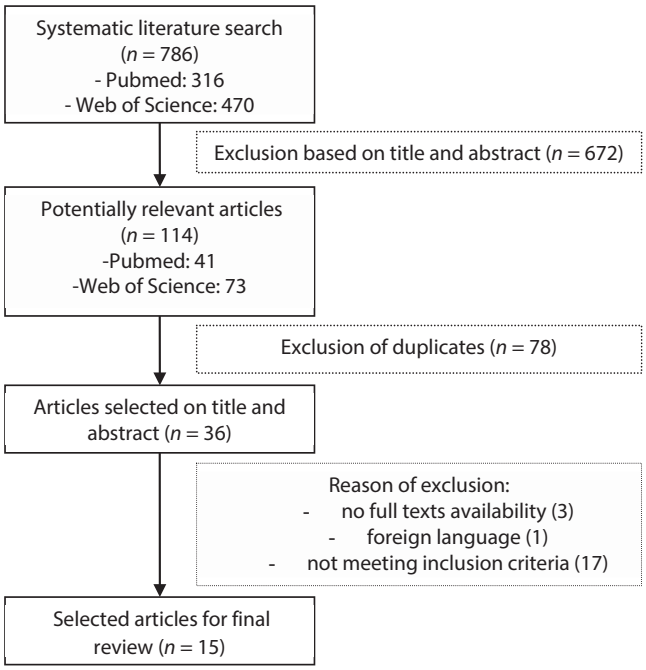

Figure 8.1. Flowchart of the selection of articles.

Virtual Reality

A small-sample (n = 4), pre and post experimental design was developed to initially study the usability and efficacy of a VR-based training program for patients with ABI (Yip & Man, 2009). Outcome measures were at the level of memory function. A VR-based community living skills training of 10 sessions were given, consisting of key cognitive training elements (including memory) to promote generalization to real-life situations. Measurements consisted of built-in parameters to document the participants' performance during each

session and the Neurobehavioural Cognitive Status Examination. Due to the explorative and qualitative character of this study, a statistical significance was not established. However, a positive training effect was shown by the outcome measures and narratively presented. All 4 patients showed improvement in skills acquisition on the community living tasks and in memory performance on neuropsychological measurements. All patients showed the same improvement in performing the tasks when tested again in a real-life environment.

Caglio et al. (2012) described a qualitative case-study of a 24-year-old man with TBI presenting memory deficits and evaluated the efficacy of a 3D interactive VR navigational training program measuring neuropsychological changes and fMRI modification cerebral activations. Measurements consisted of a functional neuroimaging assessment and a standardized neuropsychological assessment on frontal executive functions, general cognitive functions, and various memory functions (i.e., spatial short-term memory, visual-spatial learning, WM, verbal learning). Visual-spatial memory improvement appeared to be present both after the VR navigational training and in follow-up testing. The functional neuroimaging assessment showed an increased cerebral activity in the left hippocampus and the right parahippocampal cortex compared to the pre-training assessment.

Four years later, Yip and Man (2013) described the effectiveness of a VR-based memory training in a larger sample (n = 37). By using a Randomized Controlled Trial (RCT), the effectiveness was evaluated of a VR-based training program targeting prospective memory. While the experimental group received a 12-session VR-based training, the control group did not receive any training but did attend regular readings and table game activities. Neuropsychological tests were administered to measure the effects of the treatment on prospective memory skill acquisition, prospective memory, learning, and executive function. The results showed significantly larger changes in both VR-based and real-life prospective memory outcome measures after the training, indicating a transfer of learnt skills in a virtual environment to a real-life setting. Related cognitive attributes such as frontal lobe functions and semantic fluency showed a significant improvement compared to the control group.

The study of Yip and Man (2013) was considered to be of high quality. Both the studies of Caglio et al. (2012) and Yip and Man (2009) were considered to be of low quality based on the quality assessment. It should be noted, however, that a true comparison was difficult to make as 2 studies were qualitative research (Caglio et al., 2012; Yip & Man, 2009), whereas 1 was quantitative research (Yip & Man, 2013).

To sum up, although the 3 studies do identify an improvement in memory function after VR-based training, it is difficult to draw any conclusions as the number of articles available was limited. Besides, of all the articles available only 1 study was considered of high quality.

Table 8.1. Virtual Reality (VR) Overview study, intervention, patient characteristics

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Yip and Man, 2009	Small sample pre-post experimental design	4	Built-in parameters NCSE Memory Lawton IADL Self-efficacy questionnaire	Improved but NS (all patient) Improved but NS (3/4) Improved but NS (3/4) Improved but NS (3/4)	Pre Post	To test the usability and effect of newly-developed VR-based training on memory in ABI.	VR-based community living skills training program. Cognitive training elements (including memory)	35–40 min session/ 3 times a wk 10 sessions total	3 stroke 1 TBI	Not specified	8 to 30 m
Caglio et al., 2012	Case-study	1	CBTT CST Digit Span RAVLT TMT Phonemic Fluency ADAS RBMT fMRI	NS IR: .03* DR: .05* NS IR: .05* DR: NS NS NS Improved but NS Improved but NS More extended activation	Pre Post 2 m 1 y	Examining the effect of navigational training using 3D VR-based video game on spatial and verbal memory.	3D VR-based Videogame. Effective in activating hippocampal formation improving spatial and verbal memory.	90-min session/ 3 times a wk 5 wk total	TBI moderate	24	1 y

Table 8.1. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Yip and Man, 2013	Single-blind, Randomized, controlled, design (RCT)	37 (E: 19) (C: 18)	Built-in Parameter: IR DR Event Time Time checks CAM PROMT-CV HKLLT FAB WFT-CV CTT BC-PM: Event Time Ongoing task CIQ Self-efficacy questionnaire	 < .05* NS < .001**** < .001**** < .001**** < .05* NS < .01*** < .01*** NS < .01** < .01** NS NS < .01**	Pre Post	To investigate the effect of VR-based Prospective memory (PM) training program on PM function for ABI patients.	VR-based PM training program. Using every day PM activities as training content.	30-45 min session/ 2 times a wk 12 sessions total	Not specified	Exp: 37.8 SD: 10.58 Control: 38.5 SD: 11.4	E: 145.13 d SD: 97.46 C: 167.53 d SD: 149.40

Significant level $p < .05$*; significant level $p < .01$**; significant level $p < .005$ ***; significant level $p < .001$****. **Abbreviations:** years (y); months, (m); week (wk); days (d); hours (h); minute (min); seconds (s); effect size (ES); standard deviation (SD); Not Significant (NS); Experimental group (E); Control group (C); Corsi Block Tapping Test (CBTT); Corsi's Supraspan Test (CST); Rey Auditory Verbal; Learning Test (RAVLT); Immediate Recall (IR); Delayed Recall (DR); Trial Making Test (TMT); Alzheimer's Disease assessment Scale (ADAS; Riverhead Behavioral Memory Test (RBMT); Functional Neuroimaging assessment (fMRI); The Neurobehavioral Cognitive Status (NCSE); Lawton Instrumental Activities of Daily Living Scale (Lawton IADL); Chinese Version Mini Mental State Examination (MMSE-CV); Test of Nonverbal Intelligence – 3rd Edition (TONI-3); Chinese Version of the Self-Awareness of Deficit Interview (SADI-CV); The Cambridge Prospective Memory Test Chinese Version (CAMPROMT-CV); Hong Kong List Learning Test (HKLLT); Frontal Assessment Battery (FAB); Word Fluency Test (WFT-CV); Color Trail Test (CTT); Behavioral Checklist of prospective Memory Task in a real environment (BC-PM); Chinese version of the Community Integration Questionnaire (CIQ-CV).

Computer-Based Cognitive Retraining

Using a RCT, the effects of intense adaptive WM training in stroke patients were investigated (Westerberg et al., 2007). A sample of 18 patients was randomly divided into an experimental or passive control group. The experimental group was trained using computer-based visuo-spatial and auditory WM tasks at home. The training method was implemented with the software program Cogmed QM (Cognitive Medical Systems). The control group only performed the neuropsychological test battery with no training in between at baseline and after 5 weeks. Both WM and attention abilities improved significantly within the experimental group, but not within the passive control group.

In a cross-over RCT, the short- and long-term transfer effects of a computerized WM training program were evaluated for patients suffering of WM deficits after ABI (Lundqvist, Grundstrm, Samuelsson, & Rönnberg, 2010). A sample of 21 patients was randomly divided into 2 groups. The experimental group received systematic WM training (Cogmed QM), whereas the control group did not receive any training during the same period. The patients were assessed at baseline, after 4 and 20 weeks with neuropsychological tests focusing on verbal and visual WM. There was a significant improvement on the trained WM tasks and the non-trained WM task as measured by neuropsychological tests at 4 and 20 weeks after training compared to baseline.

A prospective cohort study evaluated the effectiveness of a computerized training using Cogmed QM software (B. Johansson & Tornmalm, 2012). A sample of 18 ABI patients attended the training 3 times a week. The patients were assessed before, during, after the WM training, and additionally at a 6 month follow-up with WM assessments. The computerized training showed a significant improvement on trained WM tasks. The effect was maintained at the 6 month follow-up. The study supports the idea that a computerized WM training program can affect WM functioning in ABI patients.

An additional RCT assessed the effectiveness of computerized WM training (Cogmed QM) on WM functioning in ABI patients (Björkdahl et al., 2013). A sample of 38 ABI patients were randomly assigned to an experimental group or control group and received 5 weeks of standard rehabilitation in accordance with the usual routine at the clinic. The experimental group was offered an additional training with the Cogmed QM training program. To explore the impact of the training, assessments were done at baseline, after the training program, and at a follow-up 3 months later. The assessment consisted of neuropsychological tests and a WM questionnaire measuring WM on functional level (i.e., level of activity in daily life). The experimental group improved significantly more compared to the control group. Cogmed QM showed a generalized effect on non-trained WM tasks.

By using a quasi-experimental pre-test and post-test design, the effectiveness of a CBCR program was evaluated on improving memory and attention function for patients with ABI (Li et al., 2013). A sample of 12 patients was assessed using the Cognistat Assessment as pre-test and post-test measurement. Each patient completed 8 sessions using the attention and memory subprograms of the Parrot Software, which is an interactive rehabilitation program with over 100 subprograms designed to improve cognitive function. Significant improvement was found in both memory and attention measured by the Cognistat Assessment scores.

A RCT investigated whether patients with a dysfunctional WM could improve their WM and psychological health using a computerized WM training with the Cogmed QM program (Åkerlund, Esbjörnsson, Sunnerhagen, & Björkdahl, 2013). A sample of 47 patients, in the sub-acute phase after ABI, were randomly assigned into an intervention group and a control group. Various WM neuropsychological tests were administered at baseline, post-intervention, and at a follow-up of 18 weeks. Both groups underwent integrated rehabilitation. The intervention group also attended the computerized WM training program, which was offered to the control group after the completion of the study. Both the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) and the Digit Span differed significantly between the intervention and control group due to the greater improvement in the intervention group after the WM training. Both groups improved after WM training on the BNIS, the Digit Span, and the WAIS III WM scale. Additionally, psychological health improved as both groups reported less depressive symptoms.

A RCT evaluated the effects of CBCR with regard to semantic memory, verbal fluency, and short-term auditory-verbal memory in patients with ABI (De Luca et al., 2014). A sample of 35 ABI patients were randomly divided into 2 groups. Cognitive impairment was investigated through the use of a psychometric battery, administered before and 2 months after the training. The training was given to the experimental group, in addition to conventional treatment. After the training, the results showed a global improvement in both of the groups. However, the experimental group showed a greater cognitive improvement than the control group, with significant differences in all the neuropsychological tests. The results suggest that CBCR may be a promising methodology to optimize rehabilitation outcomes following ABI.

Based on the evaluated elements from the quality assessment, the studies of Westerberg et al. (2007), Lundquist et al. (2010), and Björkdahl et al. (2013) were considered to be of high quality (see Table 8.4). The studies of Johansson and Tornmalm (2012), De Luca et al. (2014), and Åkerlund et al. (2013) were considered to be of moderate quality. The study of Li et al. (2013) was considered to be of low quality.

Table 8.2. Computer-Based Cognitive Retraining (CBCR) Overview study, intervention, patient characteristics

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Westerberg et al., 2007	Randomized, controlled, design (RCT)	18 (E: 9) (C: 9)	Span Board Digit-Span Stroop Claeson Dahl Raven's PM Word list: Repetitions DR PASAT RUFF CFQ	< .05* ES .83 < .005*** ES 1.54 NS ES .24 NS NS ES .1 NS ES .3 NS ES .05 < .001**** ES .61 < .005*** ES .81 < .005*** ES .8	Pre Post	The effect of intense, adaptive WM training on various visuo-spatial, auditory modalities after stroke.	Computer-based visuo-spatial and auditory working memory training (Cogmed QM).	40-min session 5 times a wk (90 trials a d) 5 wks total	Stroke (mild to severe)	54 SD: 7.7	12 to 36 m

Table 8.2. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Lundqvist el al., 2010	Cross-over, Randomized, controlled, design (RCT)	21 (E: 10) (C: 11)	PASAT: A1-A2 A1-A3 CWIT: A1-A2 A1-A3 Block-Span LST: A1-A2 A1-A3 Picture Span COPM: A1-A3 EQ-5D VAS	 < .001**** < .001**** < .001**** NS NS < .001**** < .001**** NS < .05* NS NS	Pre (A1), Post (A2), 20 wks (A3)	Examining the short- and long-term effects of CBCR on visuo-spatial and verbal WM.	Computer-based training visuo-spatial and verbal WM tasks (Cogmed QM).	45–60 min session/ 5 times a wk 5 wks total	1 TBI 11 Stroke 5 Infection 2 Tumor 2 SAH	43.3 SD: 9.8	46.4 SD: 31.9
Johansson & Tornmalm, 2012	Prospective cohort design	18	Built-in Parameter CFQ COPM: Perf. Satify.	< .001**** .018* .008*** .01**	During Post 6m	Effect of computer-based program on daily WM functioning in ABI.	Working Memory Training Program (Cogmed QM)	30–45 min session/ 3 times a wk 7–8 wks total	5 TBI 6 Tumor 7 Stroke	47.5 SD: 13	7y SD: 6.35

Table 8.2 continues on next page.

Table 8.2. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Björkdahl et al., 2013	Randomized, controlled, design (RCT)	38 (E: 20) (C:18)	Digit B: A1-A2 A1-A3 AMPS: A1-A3 A2-A3 RBMT II A3-A4 FIS: A1-A2 WM Q: A1-A3	 .003*** ES -.48 < .001**** ES -.56 .016* ES -.38 .038* ES -.33 .042*** ES -.51 .038* ES -.33 .006 *** ES -.44	Pre (A1), Post (A2), 18wk (A3) C: 24wks (A4)	Explore the feasibility and effect of computer-based program on memory function after ABI.	Working memory training program (Cogmed QM)	30–45 min session/ 5 d a wk 5 wks total.	28 stroke 5 TBI 5 Other	51 SD: 11	27 wks
Li et al., 2013	Quasi-experimental pre-post test design	11	Cognistat Assessment: Attention Memory	 < .005*** < .05*	Pre Post	CBCR program on improving memory and attention in ABI patients.	CBCR Parrot Software: 8 subprograms for attention and memory.	60-min session/ 10 lessons per session/ 1 session a wk 8 sessions total.	Not specified	49.45 SD: 19.02	21.27 SD: 14.21

Table 8.2. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Åkerlund et al., 2013	Randomized, controlled, design (RCT)	45 (E: 25) (C: 20)	Digit F A1-A2 A1-A3 Digit B A1-A2 A1-A3 Span board F Span Board B Span Board Scaled Score WAIS III WM scale A1-A2 A1-A3 BNIS A1-A2 A1-A3 DEX	 .003*** .002*** .004*** .0001**** NS NS NS < .001**** .003*** .006*** .006*** NS	Pre (A1), 6 wks (A2), 18 wks (A3)	Explore the effect of WM-training on WM, cognition, physiological health in ABI patients	Working memory training program (Cogmed QM).	30–45 min session/ 5 d a wk 5 wks total	E: 17 Stroke 4 TBI 4 Other C: 15 Stroke 3 TBI 2 Other	E: Median: 51 Range: 22–63 C: Median: 53 Range: 22–62	E: Median: 32 wks Range: 12–135 C: Median 22.5 wks Range: 16-–500
De Luca et al., 2014	Randomized, controlled, design (RCT)	35 (E:15) (C:20)			Pre (A1) Post (A2) 2m (A3)	Evaluate the effect of cognitive PC-training in ABI patients.	Cognitive PC-training: memory, executive functions, abilities of thinking.	24 sessions, 3 times a wk. 8 wks total.	TBI 48.57% Stroke 51.43%	E: 30.93 SD: 11.10 C: 39.75 SD:15.43.	Not Specified

Table 8.2 continues on next page.

Table 8.2. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
De Luca et al., 2014			Levels Cognitive Functioning								
			A1-A2	< .001****							
			A1-A3	.004***							
			RML								
			A1-A2	.009**							
			A1-A3	.002***							
			Attentive Matrices								
			A1-A2	.008**							
			A1-A3	< .001****							
			MMSE								
			A1-A2	.002***							
			A1-A3	.002***							
			CVF								
			A1-A2	.002***							
			A1-A3	.03*							
			LVF								
			A1-A2	.007**							
			A1-A3	< .001****							
			RAVLT IR								
			A1-A2	.001**							
			A1-A3	< .001****							
			RAVLT Recall								
			A1-A2	.009**							
			A1-A3	.007**							

Table 8.2. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measurements	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
De Luca et al., 2014			Constructional Apraxia								
			A1-A2	.03*							
			A1-A3	.002**							
			Activities Daily Living								
			A1-A2	.005**							
			A1-A3	.02*							
			IADL								
			A1-A2	.005**							
			A1-A3	.02*							
			Barthel Index								
			A1-A2	.002**							
			A1-A3	.07							
			Hamilton Anxiety								
			A1-A2	.94							
			A1-A3	.01*							
			Hamilton Depression								
			A1-A2	.009**							
			A1-A3	.009**							

Significant level $p < .05$*; significant level $p < .01$**; significant level $p < .005$ ***; significant level $p < .001$****. **Abbreviations:** years (y); months, (m); week (wk); days (d); hours (h); minute (min); seconds (s); effect size (ES); standard deviation (SD); Not Significant (NS); Experimental group (E); Control group (C); Stroop Interference Test (Stroop); Raven's Progressive Matrices (Raven's PM); Cognitive Failure Questionnaire (CFQ); Paced Auditory Serial Addition Test (PASAT); RUFF 2 & 7 Selective Attention Test (RUFF); Cogmed Cognitive Medical System (Cogmed); Colour Word Interference Test Condition 4-Inhibition/Switching (CWIT); Subarachnoidal Haemorrhage (SAH); Block-Span Board Forward and Backwards from WAIS R-NI (Block Span); Listening Span Task (LST); The Picture Span (Picture Span); Canadian Occupational Performance Measure (COPM); EQ-5D Questionnaire (EQ-5D); Health Self-Rating VAS (VAS); Assessment of Motor and Process skills (AMPS); Riverhead Behavioural Memory Test II (RBMT II); Fatique Impact Scale (FIS); Working Memory Questionnaire (WM Q); Revearsal Motor Learning (RML); Category Verbal Fluency (CVF); Letter Verbal Fluency (LVF); Rey Auditory Verbal; Learning Test (RAVLT); Immediate Recall (IR); Delayed Recall (DR); Instrumental Activities of Daily Living Scale (IADLC).

To sum up, the 7 studies reported a significant improvement of the memory function after the completion of CBCR. As 6 studies were considered of moderate/high quality, these findings support the idea that CBCR may be a promising methodology to optimize the recovery of the memory function in ABI patients.

Non-Invasive Brain Stimulation

A single-blind, cross-over, and sham-controlled study investigated whether anodal tDCS over the left dosolateral prefrontal cortex would affect the WM performance of post-stroke patients (Jo et al., 2009). A sample of 10 patients participated in 2 stimulation conditions (anodal stimulation with a constant current of 2 mA and sham stimulation). The order of stimulation was randomly assigned. Each stimulation session was separated by at least 48 hours to wash out the effects of the previous run. All patients performed a two-back WM task before and after the administration of the tDCS. A significant improvement in accuracy and recognition accuracy was only found in the anodal tDCS and not in the sham tDCS. Anodal tDCS applied over the left dorsolateral prefrontal cortex at an intensity of 2 mA was associated with enhanced verbal WM performance in patients with stroke.

A double-blind RCT examined whether rTMS applied over the left dorsolateral prefrontal cortex affected cognition and mood in post-stroke patients (Kim, Kim, Chun, Yi, & Kwon, 2010). A sample of 18 patients were enrolled and randomly assigned to 1 of 3 treatment groups: low-frequency (1 Hz) stimulation, high-frequency (10 Hz) stimulation, and sham stimulation (control). Each patient underwent 10 consecutive treatment sessions (5 times a week for 2 weeks). A complete neuropsychological battery was performed to evaluate various domains of cognition such as verbal and visual memory, executive functioning, attention, working memory, and visuomotor coordination. The Beck Depression Inventory was used to assess mood status. These assessments were conducted in all patients before and after treatment. Treatment had no significant effect on any cognitive function parameter in any of the 3 groups. In contrast, high-frequency rTMS resulted in significantly lower Beck Depression Inventory scores compared with baseline and compared with the other 2 groups. These preliminary data suggest that there was a positive effect on mood, but the study was not powered to detect any measurable effect on memory.

A double-blind RCT investigated the synergistic effects of both computer-assisted cognitive rehabilitation (CACR) and tDCS on cognitive function (attention and memory) in post-stroke patients (Park, Koh, Choi, & Ko, 2013). A total of 11 patients were randomly divided into an active tDCS group and a control group. Both groups received CACR training for 30 minutes a day (15 minutes memory training, 15 minutes attention training) 5 times a week

until discharge. The tDCS group completed the CACR program during a mean period of 18.5 days combined with the anodal tDCS (over the bilateral prefrontal cortex). The control group also completed the CACR program (mean period of 17.8 days) combined with tDCS, except that the current was reduced to 0 after 30 seconds. All patients were evaluated using the Korean Mini-Mental State Examination and the Seoul Computerized Neuropsychological Test (SCNT). The SCNT was composed of 10 measurements, assessing the verbal memory, visuospatial memory, attention, and visuo-motor coordination. The patients of the tDCS group showed a significant improvement in 2 attention tests of the SCNT items. The results indicated that the combined use of tDCS and a CACR program may provide beneficial effects in improving attention. However, no evidence was found for the memory function.

A double-blind RCT investigated the cumulative effects of anodal tDCS on EEG oscillations, attention, and WM function among patients with TBI (Ulam et al., 2015). A sample of 26 patients were randomly assigned to active or sham tDCS groups. EEGs were recorded at 6 different time points, assessing both immediate and cumulative effects of tDCS on EEG oscillations. Twenty-minutes sessions of 1 mA anodal tDCS over the left dorsolateral prefrontal cortex were provided on 10 consecutive days for the active group. For the sham tDCS group, current gradually faded in over a period of 8 seconds, followed by 30 seconds of stimulation, with the current then fading out over an additional 8 seconds. Neuropsychological tests were administered before and after the series of tDCS sessions. While attention and WM were the primary interest, other outcome measures were included. Results showed that no between-group differences were present for any of the tests administered. Both the active tDCS and sham tDCS showed an equal number of statistically significant improvements (15 out of 19 tests). The EEG revealed immediate and cumulative changes in brain oscillations for the active tDCS, but not in the sham group. Results suggest that 10 anodal tDCS sessions may beneficially modulate regulation of cortical excitability for patients with TBI. However, tDCS does not show greater improvements on neuropsychological test (including measurements of WM) compared to sham tDCS.

A double-blind RCT determined whether cumulative anodal tDCS over the left dorsolateral prefrontal cortex could enhance rehabilitation of memory and attention in patients with TBI (Leśniak, Polanowska, Seniów, & Członkowska, 2014). A sample of 23 patients were randomly assigned to 2 groups. The experimental group received anodal tDCS (10 minutes of 1 mA) on a daily basis for 15 days followed by rehabilitative cognitive training. The control group received anodal tDCS in the first 25 seconds of a 10 minute stimulation period (sham condition) with the same rehabilitative cognitive training. A battery of neuropsychological tests targeting memory and attention was administered (visual and auditory modalities). Participants were tested twice before the intervention (to control for spontaneous recovery),

Table 8.3. Non-Invasive Brain Stimulation (NBS) Overview study, intervention, patient characteristics

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Jo et al., 2009	Single-blind cross-over, sham-controlled design	10	2-back verbal WM task: Accuracy Recognition Response time	 < .05* < .05* NS	Pre Post	Effect of Anodal tDCS over left DLPFC on WM after stroke.	tDCS constant current of 2 mA over DLPFC. 48hr interval. Sham stimulation.	30-min session/ two conditions: Anodal / sham stimulation.	10 Stroke	47.9 SD: 8.7	Not specified
Kim et al., 2010	Double-blind, Ran-domized, sham-controlled design (RCT)	18 (1 Hz: 6) (10 Hz: 6) (C: 6)	Digit F Digit B Forward visual span Backward visual span Verbal learning test Visual learning test Auditory CPT Visual CPT Word of color word test Color of color word test Tower of London test MBI BDI	NS NS NS NS NS NS NS NS NS NS NS NS NS	Pre Post	Effect of rTMS over left DLPFC on cognition and mood in post-stroke patients	Group 1 1-Hz stimulation at 80% MT. Group 2 (10 Hz) 10-Hz stimulation at 80% MT. Control group Sham stimulation was delivered as 1HZ protocol except the angle of the coil was at 90% perpendicular to the skull.	G1: 3 trains of 5min duration each, separated by 1min pauses. Total period of 20 min (a total of 900 pulses). G2: 3 blocks, separated by 10-min interval. Each block: 15 trains of 1s duration separated by 10 s pauses (a total of 450 pulses)	18 Stroke	Group 1 63.3 SD: 7.4 Group 2 53.5 SD: 16.9 Control 66.8 SD: 17.2	Group 1 404.4 d SD 71.7 Group 2 241.2 d SD: 42.5 Control 69.7 d SD: 39.0

Table 8.3. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Park et al., 2013	Double-blind, Ran-domized, Sham-controlled design (RCT)	11 (E: 6) (C: 5)	SCNT		Pre Post	Effect of anodal tDCS combined with CACR to improve cognitive function.	CACR: 15-min memory training and 15-min attention training. 30 min a d/ 5 d a wk/ until discharge	Active Anodal tDCS over bilateral PFC (2mA) for 30 min. Control: tDCS over bilateral PFC (2mA) for 30 s.	11 Stroke	Active: 65.3 SD: 14.3 Sham: 66.0 SD: 19.8	Active: 29.0 d SD: 18.7 Sham: 25.2 d SD: 17.5
			Digit F	.429							
			Digit B	.931							
			Visual span forward	.931							
			Visual span backward	.931							
			Auditory CPT	.017*							
			Auditory controlled CPT	.792							
			Visual CPT	.017*							
			Visual controlled CPT	.792							
			MMSE	.931							
Ulam et al., 2014	Double-blind, Rand-omized, controlled design (RCT)	26 (E: 13) (C: 13)	Elevator count w distraction	.945	Pre Post	Effect of anodal tDCS over DLPFC on attention and WM on EEG oscil-lations and neuropsycho-logical tests in TBI.	tDCS constant current of 1 mA anodal on DLPFC	20-min session/ 10 d/ One session a d.	26 TBI	Active: 31.34 SD: 9.8 Sham: 35.70 SD: 14.7	Active: 57.38 d SD: 37.8 Sham: 41.08 SD: 20.87
			Visual elevator accuracy	.003***							
			Visual elevator time	.035*							
			Elevator count w reversal	.008**							
			Digit F	.71							
			Digit B	.034*							
			Digit S	.0001****							
			Symbol span	.0001****							

Table 8.3 continues on next page.

Table 8.3. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Ulam et al., 2014			Color naming time	.002***							
			Word reading time	.011*							
			Inhibition time	.001****							
			Inhibition accuracy	.0001****							
			Inhibit/switch time	.004***							
			Inhibit/switch accuracy	.001****							
			TASIT	.0002****							
			HVLT total recall	.26							
			HVLT delayed recall	.06							
			BVMT total recall	.006**							
			BVMT delayed recall	.03*							
Lešniak et al., 2014	Double-blind, Sham-controlled design	23 (E:12) (C:11)	RAVLT Learning RAVLT Delayed recall RAVLT Delayed recognition	.1 ES .36 Sham .93 ES .02 tDCS .21 ES .26 Sham .95 ES .01 tDCS .21 ES .26	3 wk before, Pre Post 4 m	Effect of repeated application of anodal tDCS would enhance the effects of specific cognitive training to improve memory and attention in TBI.	Cognitive computerized training using internal strategies. Prior to each session, the patient received either active or sham anodal tDCS. (1 mA over DLPFC)	Active: 15 sessions of anodal tDCS (1 mA)/ 10 min/ current density = 0.028 mA/ cm^2. Control: 15 sessions of sham anodal tDCS (1mA for 25 s).	23 TBI	Active: 28.3 SD: 9 Sham: 29.3 SD: 7.7	Active: median: 10.8 m range: 5.8-18.5 Sham: median 13.2 m range: 6.5-25.1

Table 8.3. *Continued*

Study characteristics						**Intervention characteristics**			**Patient characteristics**		
Authors	Design	Number of patients	Outcome measures	*p*-value	Measure-ments	Aim	Intervention	Duration/ intensity	Diagnostic criteria	Mean age	Time after onset
Lešniak et al., 2014			PRM Immediate recall	Sham .07 ES .38 tDCS .23 ES .25							
			PRM Delayed Recognition	Sham .18 ES .29 tDCS .23 ES .25							
			PASAT	.06 ES .31							
			SSP	Sham .27 ES .23 tDCS .03* ES .43							
			RVP	.007 ** ES .66							
			EBIQ	.41							

Significant level $p < .05$*; significant level $p < .01$**; significant level $p < .005$ ***; significant level $p < .001$****. **Abbreviations:** years (y); months, (m); week (wk); days (d); hours (h); minute (min); seconds (s); effect size (ES); standard deviation (SD); Not Significant (NS); Experimental group (E); Control group (C); Low frequency Stimulation (LFS); Dorsolateral Prefrontal Cortex (DLPFC); Motor Threshold (MT); Beck Depression Inventory (BDI); Continuous Performance Test (CPT); Modified Barthel Index (MDI); Verbal Associate Learning Test (Verbal ALT); Digit Span Forward (Digit F); Digit Span backward (Digit B); Digit span sequencing (Digit S); Visual Associate Learning Test (Visual ALT); Visual Associate Learning Test Taping forward (VALT Tap F); Visual Associate Learning Test Taping Backward (VALT Tap B); Vigilance Continuous Performance Test (VCPT); Mini-Mental Status Examination (MMSE); Hopkins Verbal Learning Test (HVLT); Brief Visual Memory Test (BVMT); Rey's Auditory Verbal Learning Test (RAVLT); Pattern Recognition Memory Test (PRM) Paced Auditory Serial Addition Test (PASAT); Spatial Span Test (SSP); Rapid Visual Processing (RVP).

Table 8.4. Scores of the quality assessment of the discussed studies, based on 8 elements

Study	1	2	3	4	5	6	7	8	Total score	Quality	Aim
Yip & Man, 2009	0	0	0	0	1	0	0	1	**2**	**Low**	Feasibility
Caglio et al., 2012	0	0	0	0	1	0	0	1	**2**	**Low**	Feasibility
Yip & Man, 2013	1	1	0	1	1	1	0	1	**6**	**High**	Effectiveness
Westerberg et al., 2007	1	1	1	1	1	0	1	1	**7**	**High**	Effectiveness
Lundqvist et al., 2010	1	1	0	0	1	1	1	1	**6**	**High**	Effectiveness
Johansson & Tornmalm, 2012	0	0	0	0	1	1	0	1	**3**	**Moderate**	Feasibility
Björkdahl et al., 2013	1	1	0	0	1	1	1	1	**6**	**High**	Effectiveness
Li et al., 2013	0	0	0	0	0	1	0	1	**2**	**Low**	Effectiveness
Åkerlund et al., 2013	1	1	0	0	1	1	0	1	**5**	**Moderate**	Effectiveness
De Luca et al., 2014	1	1	0	0	1	1	0	1	**5**	**Moderate**	Effectiveness
Jo et al., 2009	1	0	1	0	1	1	0	0	**4**	**Moderate**	Effectiveness
Kim et al., 2010	1	1	1	1	0	0	0	1	**5**	**Moderate**	Effectiveness
Park et al., 2013	1	1	1	1	0	0	0	1	**5**	**Moderate**	Effectiveness
Ulam et al., 2014	1	1	1	1	1	1	1	0	**7**	**High**	Effectiveness
Leśniak et al., 2014	0	1	1	1	1	1	1	1	**7**	**High**	Effectiveness

Note. 0 = negative; 1 = positive. High was considered total scores ≥ 6, moderate ≥ 3 and ≤ 6, and low ≤ 3. Elements: (1) Randomization of intervention or different condition: (2) Comparison of an experimental group and a control group; (3) Blinding of participants; (4) Blinding of researchers; (5) Reporting completeness of follow-up; (6) Group size ≥ 10 per group; (7) Reporting effect size; (8) Reporting time post-ABI.

after the intervention, and 4 months later. After treatment the experimental group exhibited larger effect sizes in 6 of 8 cognitive outcome measures, but they were not significantly different from controls. At follow-up, differences remained insignificant. This study did not provide sufficient evidence to support the efficacy of repeated anodal tDCS for enhancing rehabilitation of memory and attention in patients after severe TBI.

Based on the quality assessment the studies of Ulam et al. (2014) and Leśniak et al. (2014) were considered to be of high quality. The studies of Jo et al. (2009); Kim et al. (2010), and Park et al. (2013) were considered to be of moderate quality.

To sum up, only 1 study (Jo et al., 2009) detected a significant enhanced verbal WM performance after the use of NBS in stroke patients. Four studies (Kim et al., 2010; Leśniak et al., 2014; Park et al., 2013; Ulam et al., 2015) did not find sufficient evidence to support the efficacy of NBS for enhancing rehabilitation of memory in ABI patients.

Discussion

The aim of this systematic review was to describe memory rehabilitation interventions based on *remediation*-oriented techniques post ABI and evaluate its effectiveness. We found 15 studies in the last 7 years (2007–2014), evaluating 3 memory *remediation* approaches; 3 studies on VR, 7 on CBCR and 5 on NBS. Considering the quality of the studies, only 1 study representing VR, 3 studies representing the NBS technique, and 5 studies representing CBCR fulfilled the RCT requirements. It appeared, based on the quality assessment that CBCR was the most promising as the methodological quality was high. Importantly, CBCR is found effective in improving the memory function post ABI. Although the VR studies did find a positive effect, there was only a low number of studies available and the quality of the studies was also considered low. Four of the 5 studies evaluating NBS did not find significant improvement of the memory function and the quality of these studies were considered moderate to high. Only 1 of the studies evaluating NBS did find positive results, yet the quality of this study was considered moderate. More details of the findings will be discussed below for each technique separately.

Computer Based Cognitive Rehabilitation

All 7 studies have shown that CBCR can be effective in improving memory function in individuals with ABI (Åkerlund et al., 2013; Björkdahl et al., 2013; De Luca et al., 2014; B. Johansson & Tornmalm, 2012; Li et al., 2013; Lundqvist et al., 2010; Westerberg et al., 2007). These findings are consistent with the prediction of Klingberg, (2010), suggesting that WM training could be used as a *remediation*-oriented intervention for individuals for whom low WM capacity is a limiting factor in everyday life.

Five studies (Björkdahl et al., 2013; De Luca et al., 2014; B. Johansson & Tornmalm, 2012; Lundqvist et al., 2010; Westerberg et al., 2007) investigated the generalized effect on functional level (i.e., level of activity in daily life) and found a positive effect. This was measured subjectively, using self-report questionnaires regarding daily activities relying on the memory function. This is interesting from a transfer-of-training point of view. Five studies measured the long-term effects, ranging from 18 to 24 weeks post-intervention and found positive results (Åkerlund et al., 2013; Björkdahl et al., 2013; De Luca et al., 2014; B. Johansson & Tornmalm, 2012; Lundqvist et al., 2010).

Five studies randomly assigned their participants to an experimental versus a control group and therefore fulfilled the RCT requirements. Only 1 study used a double blind design (both patient and researcher were blind to the treatment of the patient) (Westerberg et al., 2007). Future research should focus on the establishment of several other criteria such as blinding of participants and researchers to strengthen the evidence.

In conclusion, we consider CBCR as most promising due to the positive results and the relatively high methodological quality of the selected studies. However, before proposing CBCR as rehabilitation intervention in clinical practice important criteria should be fulfilled. Future research should further define the effect of the intervention generalized to functional level, participation in society level, as well as the long-term effects and the effect on quality of life. Additionally, RCT's are needed focusing on several methodological criteria to strengthen evidence.

Virtual Reality

All 3 studies found a significant improvement of the memory function after a VR-based training (Caglio et al., 2012; Yip & Man, 2009, 2013). These positive findings are consistent with findings in elderly participants with memory deficits (Optale et al., 2010). This suggests that VR-based training could possibly be a valid approach to promote memory recovery for individuals with memory deficits.

Two studies also found a generalization of the effect to a real-life environment (Yip & Man, 2009, 2013). Patients showed the same improvement in performing the tasks when tested again in a real-life environment. As such, VR-based training seems to be able to retrain the underlying function in a virtual environment and facilitate the generalization to real-life performance.

No study investigated the effect of the training on functional level. Long term effects at 2 months and 1 year post-intervention were established in the study of Caglio et al., (2012), but should be interpreted with caution due to the low methodological quality (total score: 2). Both studies of Yip and Man (2009, 2013) have shown positive effect but for a limited time-window, namely directly post-intervention as no follow-up was performed at a longer interval post-training. In future studies, it would be desirable to extend the measurements to establish the effect on functional level and the long-term effects. This could provide valuable information for clinical use.

It is important to note that the quality of the studies representing VR was low to moderate according to our quality assessment. Only 1 study (Yip & Man, 2013) met the RCT requirements and used a single blind design (blinding the researcher for the treatment). Two studies failed to apply a control group in their methodology. As a result, those studies did not blind their participants nor their researchers. Future research should involve true replication studies, taking into account essential criteria such as randomization and the use of a control group to obtain higher methodological quality.

In conclusion, despite the positive findings these results should be considered preliminary because of the limited number of studies available and the low number of ABI patients. The significant improvement on memory performance for ABI patients is promising, yet insufficient evidence is available to be proposed as treatment in clinical practice.

Non-Invasive Brain Stimulation

Four studies did not detect significant improvement in the memory function after the use of NBS (Kim et al., 2010; Leśniak et al., 2014; Park et al., 2013; Ulam et al., 2015). According to the quality assessment these studies were considered moderate to high (total score ranging from 4-7). Only 1 study found a significant WM improvement (Jo et al., 2009), however the methodological quality of this study was considered moderate (total score: 4).

These disappointing findings were unexpected due to the promising findings in healthy participants. Several studies did find significant improvement in memory tasks due to NBS in healthy participants (Kessels, D'Alfonso, Postma, & De Haan, 2000; Luber et al., 2007; Oliveri et al., 2001; Preston, Anderson, Silva, Goldberg, & Wassermann, 2010). A recent review detected positive effects of rTMS and tDCS improving measures of WM performance, including reaction time and/or accuracy (Brunoni & Vanderhasselt, 2014). These results were only found when the NBS was applied over the dorsolateral prefrontal cortex (DLPFC) (Brunoni & Vanderhasselt, 2014). On the contrary, 3 studies of the current review did not detect significant improvement of the memory function, even when NBS was applied over the DLPFC (Kim et al., 2010; Leśniak et al., 2014; Ulam et al., 2015). Additionally, positive results were found in healthy elderly adults, whereas a significant improvement was found in accuracy of a verbal WM task due to anodal tDCS as compared to sham tDCS (Park, Seo, Kim, & Ko, 2014). Unfortunately, the selected studies of this review did not find any of these findings in the ABI population except for 1 study (Jo et al., 2009). On the other hand, it is important to note that a healthy or an aging brain could possibly react very differently compared to the restoration mechanism of a damaged brain post ABI.

In conclusion, more research is needed to further explore the possibility of NBS as a *remediation*-oriented intervention of memory function post ABI.

To summarize, on the basis of this review CBCR is considered the most promising novel approach of the last decade in view of the positive results and the high methodological quality of the studies. The number of studies representing VR was limited and the methodological quality low, therefore the results should be considered preliminary. The studies representing NBS did not find evidence that the use of NBS could improve memory function and these studies were considered of moderate to high quality. Therefore, on the basis of the knowledge

available we recommend CBCR as promising *remediation*-oriented intervention intervention to improve memory function post ABI.

Strengths and limitations

This review stresses some important limitations of the literature available on *remediation*-oriented memory interventions after ABI. First, the ability to benefit of those techniques may vary depending on what kind of injury the individual suffers from (Fish et al., 2008). This review focused on memory impairment in a heterogeneous ABI patient population group with different injury-related diagnoses. This could be considered as a limitation, as each brain injury has a different pathology (e.g., focal vs. diffuse) and different demographics (e.g., age), which result in different restoration mechanisms such as different time courses and magnitudes of recovery. TBI is associated with a hallmark pattern of pathology concerning direct damage to frontal and temporal lobes, plus diffuse axonal injury resulting from tearing and shearing mechanisms (Levine et al., 2006). This causes a reduction in grey and white matter and impairs connectivity. The focal damage resulting from stroke is more diverse. In addition to a difference in pathology, the demographics of TBI and stroke are divergent. Stroke primarily affects people over 65 years of age, whereas TBI incidence is highest in the 15-24 age group. This difference in pathology and demographics result in different restoration mechanism. It would therefore have been preferable to make a distinction between TBI and stroke. However, we believe that selecting the ABI population for this review gave the possibility to collect a wider range of knowledge.

Second, sample size is a crucial issue in quantitative research which seeks to make statistically based generalizations from the study results to the wider ABI population. The sample sizes used in the available literature may be considered too small to draw firm conclusions. As well as the regular absence of a control condition, the lack of blinding of participants and researchers, and the explorative character of several studies. These limitations restricted the reliability of the study's conclusions and consequently restricted the ability for us to draw well-founded conclusions.

A major strength of our review is the inclusion of 15 studies that had not been evaluated in previous reviews. On the other hand, a limitation of this review may be the selection of appropriate search terms. We only searched on the terms *Acquired Brain Injury*, *(Traumatic) Brain Injury* or *Stroke*. This selection of search terms may be quite limited, as ABI is a collective term for many more injury-related diagnoses. The collective term ABI can be subdivided into two categories: traumatic brain injury (TBI; i.e., external force traumatically injures the brain due to accidents, assaults or neurosurgery) or non-traumatic injury derived from either

an internal source (NTBI; i.e., stroke, brain tumour) or an external source (e.g. poisoning, substance abuse). The selected search terms may have failed to cover the complete ABI population, even if the majority of ABI is caused by TBI or stroke. It might therefore be possible that we missed relevant studies.

A second limitation of this review may be the selection of the inclusion criteria. Solely studies evaluating interventions, with the focus primarily on improving the memory function were selected. Consequently, several studies may have been excluded that used neuropsychological memory assessments but had a different primary outcome measure (e.g., depression). These studies were excluded as they did not meet our inclusion criteria, although their findings might have been possibly relevant to our review.

A final limitation may be the fact that we did not focus on pharmacological interventions, even though medication could be considered a *remediation*-oriented intervention. The included pharmacological interventions could have had favourable and interesting effects on the memory function. Hence, this should be considered in future research. However, in case of this particular review, we feel that pharmacological therapies were not suitable for targeting only the memory function without affecting other cognitive function.

Conclusions

The research on *remediation*-oriented interventions reviewed in this study represents just the beginning of a new research field that explores innovative possibilities for enhancing memory function in ABI patients. Even though CBCR in particular shows great promises, more research is needed to establish this *remediation*-oriented program as standard intervention in clinical practice, especially given the heterogeneity of ABI, time course of spontaneous recovery, timing of training after ABI, and generalization of effects at several levels of functioning. Although replication studies may seem less appealing, they are sorely needed in this field where many topics are novel and risk to remain novel (Fasotti & van Kessel, 2013).

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On the morning of April 19th in 2015, I felt a tingling sensation in my left arm. I thought that I felt tired, so I laid down on the couch in my living room. My wife saw me moving strangely. She called the general practitioner who immediately sent an ambulance. I was taken to the hospital where I was admitted for a week and a half. The medical doctors told me I had a stroke. Because the left side of my body was paralyzed, I was referred to a rehabilitation center. At the beginning, I had to get used to the fact that I was admitted. The rehabilitation center felt like a prison. Looking back, it probably had something to do with the fact that I felt like a prisoner in my own body and wheelchair. After a while it started to feel like a home. Therapists started to feel like acquaintances, because I saw them on a daily basis. A year after I returned home, I went back for a follow-up appointment and my physical therapist still recognized me from afar. She waved at me in a very friendly and outgoing manner from the other end of a long corridor. It was a warm welcome back. I currently do the same work as before, but I am not as talented as I once was. I was diagnosed with an attention disorder, which means I need more time for a lot of things. I cannot trust my own perception completely, so I have to verify my interpretations with colleagues. When I start a project with new clients, I usually tell them about what happened to manage expectations. They are mostly really understanding. Over the years, I participated in two research projects that required people who had a stroke. If I can, why wouldn't I contribute to scientific research?

Chapter 9

General discussion

Objectives and main findings

Our current tools for cognitive assessment often lack sensitivity and ecological validity. It is, however, of utmost importance that neuropsychological tests are sensitive enough to assess (mild) cognitive impairment, also because a treatment plan is formulated based on the test results. In addition, the test results of the current tools do not translate easily to daily life, which makes it challenging for neuropsychologists to make recommendations concerning daily life.

The general objective of this dissertation was to investigate the use and added value of novel instruments in cognitive rehabilitation for patients with acquired brain injury (ABI). To achieve this objective, we formulated three aims: (1) to develop an instrument to systematically assess cognitive complaints in daily life; (2) to investigate the use of a digital version of existing tests to measure cognitive function, and to capitalize the opportunities afforded by digital tests by developing novel outcome measures; (3) to investigate the use and added value of technology to assess cognitive function in a more sensitive and dynamic manner, and to inventory the use of technology to improve cognitive function.

In this dissertation, I describe the first steps that are undertaken to use and benefit from novel instruments to assess and treat cognitive impairment. Although this dissertation may address the tip of the iceberg, it reveals promising areas for further refinement. We developed an inventory to systematically assess cognitive complaints in daily life, which reduces the chance that complaints are missed, or that an increase or improvement of complaints remains unnoticed (**Chapter 2**). The use of a digital neuropsychological assessment (d-NPA) was found feasible in patients with ABI (**Chapter 3**). Moreover, digital tests were shown to be of added value in assessing cognitive processes that cannot be objectified with paper-and-pencil tests (**Chapter 4**). A conceptual distinction between static tests (e.g., paper-and-pencil tests) and dynamic tests (e.g., observational scales, ecological-valid tests) was found, which provides insights into different phenotypes of visuo-spatial neglect (**Chapter 5**). By applying Virtual Reality (VR) in the assessment of visuo-spatial neglect, we found that 6–29% of patients did not show neglect on traditional tests but did show neglect on a VR-based task (**Chapter 6**). Non-immersive VR (computer monitor) as well as immersive VR (head-mounted display) was found feasible in stroke patients (**Chapter 7**). Finally, computer-based cognitive retraining and VR-based training were found promising in improving memory function (**Chapter 8**).

Discussion of the main findings

Holistic view on cognitive functioning

It is now generally accepted that health and functioning are the result of an interaction between biological, psychological, and social factors (Wade & Halligan, 2017). A biopsychosocial framework is especially implemented in rehabilitation medicine, where a multidisciplinary team addresses a wide range of factors related to functioning (Wade, 2020). The World Health Organization published the International Classification of Functioning, Disability and Health (ICF), which is explicitly related to a biopsychosocial framework (World Health Organization, 2001). The ICF enables a holistic evaluation and interpretation of functioning by distinguishing three levels: body function and structure (i.e., impairments due to loss in function), activities (i.e., functional limitations), and participation (i.e., restrictions that limits the fulfilment of a role in society). Personal factors and environmental factors may further influence functioning on these different levels. The ICF enables us to form a holistic view of a patient, which seems crucial when assessing and treating cognitive functioning (Arthanat, Nochajski, & Stone, 2004; Lexell & Brogårdh, 2015). When applied to cognition, impairments (e.g., memory impairment) may lead to limitations (e.g., difficulties remembering past conversations), and these limitations may lead to restrictions (e.g. not being able to work) (Rose, Brooks, & Rizzo, 2005). See Figure 9.1 for the use of the ICF in cognitive assessment, including our assessment tools as an example.

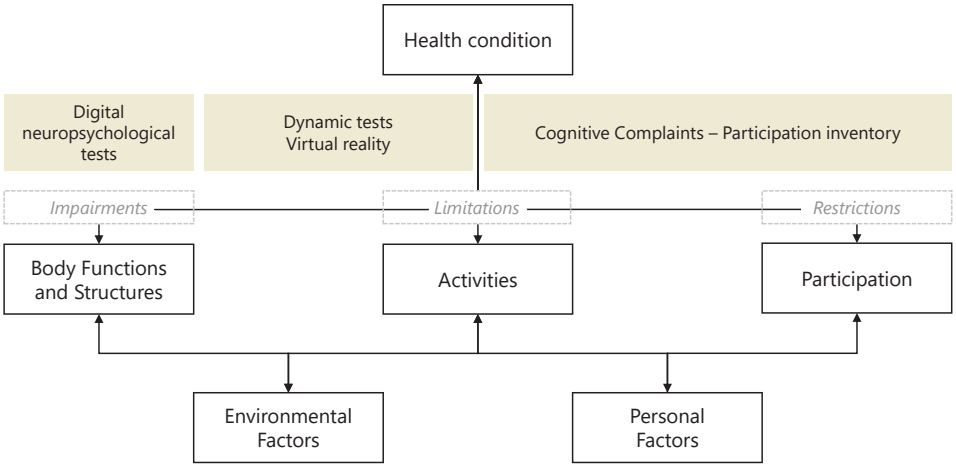

Figure 9.1. The International Classification of Functioning, Disability, and Health (ICF) enables a holistic view of cognitive functioning. Our assessment tools are shown in the model as an example.

Assessing cognitive functioning at different levels is a necessity for neuropsychologists, both in research and clinical practice. In behavioural research, experimental paradigms have been developed to unravel cognitive processes, resulting in various experimental tasks. The different outcome variables have been linked to specific cognitive processes, often embedded in theories and models (Kessels, 2019). However, the degree in which outcome measures of experimental paradigms are related to real-life behaviour remains largely unclear (Kessels, 2019; Negut, Matu, Sava, & David, 2016). In clinical practice, neuropsychological paper-and-pencil tests are generally used to assess cognitive function. Digital tests allow for the detection of more subtle cognitive impairment that are not easily objectified with paper-and-pencil tests. Neuropsychological tests (paper-and-pencil and digital) are extremely useful to differentiate between cognitive domains and subdomains. However, neuropsychological tests are merely measures of cognitive function at the level of "body function and structure". Performances on these tests do not reflect overall functioning.

For this reason, ecological-valid tests have been developed that are conducted in the real-world, such as the Multiple Errands Test (Shallice & Burgess, 1991) or the Executive Secretarial Task (Lamberts, Evans, & Spikman, 2010). A limitation, however, is the lack of a standardized and controlled setting, which results in an inconsistent degree of distractions within and between assessments. With VR, ecological-valid tests can be developed without losing control over stimulus presentation (Parsons, 2015; Rizzo, Schultheis, Kerns, & Mateer, 2004). Virtual environments resemble real-life environments and replicate the challenges found in daily life situations, while maintaining standardized protocols. In the context of developing experimental paradigms, VR provides researchers with a unique combination of extensive design possibilities, allowing patients to explore the test environment and permitting natural behaviour (Bohil, Alicea, & Biocca, 2011; Krohn et al., 2020). VR allows researchers to address many questions by capturing performance in a controlled environment that would simply not be possible by studying performance in the real-world. From a clinical point of view, VR-based tasks were found sensitive in detecting cognitive impairment by discriminating patients from healthy participants (Negut et al., 2016; Spreij et al., 2017). VR-based tasks may not only assess cognitive impairment at the level of "body function and structure", but also functional limitations at the level of "activities". For instance, a VR-based grocery task may consist measures of cognitive function, such as memory (i.e., remembering the products) or planning (i.e., chosen route through the supermarket), as well as measures of cognitive skills, such as money management (i.e., paying at the counter) or meal preparation (i.e., selecting ingredients).

Furthermore, restrictions in participation are most frequently assessed with self-report measures (Seekins et al., 2012). It is increasingly recognized that the perspective of patients

is essential in understanding and measuring a patient's functioning (Meadows, 2011). We assessed the perspective of patients and relatives by systematically assessing cognitive complaints during several daily life activities. The CoCo-P inventory gives insight on cognitive functioning at the level of "activities" and "participation". The CoCo-P can be used to capture subjective cognitive difficulties patients encounter, and, just as important, to assess the impact of these difficulties on participation.

It is important to bear in mind that personal factors (e.g., personality traits, coping styles, resilience, affective disturbances) and environmental factors (e.g., availability of services, social support, vocational modifications) influence cognitive functioning on the three levels of the ICF. For example, psychological resilience was related to fewer restrictions in participation (Wardlaw, Hicks, Sherer, & Ponsford, 2018). Moreover, barriers regarding the availability of transportation and government policies were reported to have a great impact on participation (Whiteneck, Gerhart, & Cusick, 2004). Patients with ABI may report a range of personal and environmental factors influencing cognitive functioning, so describing these facilitators or barriers seems crucial in cognitive assessment. Understanding and identifying the role of personal and environmental factors are essential, so treatment may be directed to reduce their negative effect.

In conclusion, the ICF enables a person-centered approach by focusing on all factors that influence cognitive functioning. I primarily focussed on measuring cognitive functioning at the level of "body function and structure", "activities", and "participation". Personal and environmental factors should also be taken into account to enable a holistic point of view on cognitive functioning.

Generalizability to other clinical populations

Rehabilitation may benefit any patient with a long-lasting disability, arising from any cause, at any stage of the illness, and at any age (Wade, 2020). We included patients with ABI, where cognitive impairment is a common issue. Cognitive impairment is a common issue in other clinical populations as well, but continues to be under recognised. Neuropsychological assessment has been increasing in various clinical populations, such as cardiac, oncological, as well as infectious conditions (e.g., HIV). Evidence suggests that 25–74% of patients with heart failure (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007), 15–50% of cancer survivors following chemotherapy (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012), and 30–60% of HIV-infected patients suffer from more subtle cognitive impairment (Grant, 2008). Another clinical population are patients with post intensive care syndrome (PICS), where cognitive impairment occur in 25% of the patients (Rawal, Yadav, & Kumar, 2017). All these clinical populations present a wide variety of clinical

manifestations. Manifestations of cognitive impairment are still poorly recognized in clinical practice. Patients who hold professional and social positions, may report forgetfulness or concentration difficulties which drastically affect their ability to fulfil work and social responsibilities. It is important to note that even mild cognitive impairments may have a devastating impact on daily life. Patients reporting cognitive complaints should be referred for neuropsychological assessment to unravel the cognitive strengths and weaknesses and to formulate an appropriate treatment plan. Furthermore, in patients with neurodegenerative diseases or dementia, an early diagnosis is essential so patients and relatives have access to treatment and support. In order for an early detection to occur, tools must be sensitive to mild cognitive impairment (Lesk, Wan Shamsuddin, Walters, & Ugail, 2014). Interestingly, the criteria of dementia entails that cognitive impairment must interfere with daily life activities. Assessing cognitive functioning on different levels of the ICF seems therefore a necessity in patients with dementia. Neuropsychological paper-and-pencil tests or cognitive screening instrument remain the "gold standard" in clinical care. However, a more holistic approach to assess cognitive functioning may further improve the care of these patients.

Methodological considerations

Study population

We included patients with ABI, which is the largest population in rehabilitation medicine in the Netherlands (Revalidatie Nederland, 2017). We mainly collected data of patients with stroke and traumatic brain injury (TBI) as these are the most common causes of ABI. In Chapter 5, 6 and 7, we collected data of stroke patients who were referred for inpatients rehabilitation care. In these patient, a safe discharge from hospital to home is not achievable but is expected to be achievable after inpatient care. This is a relative selective group as these patients have to be vital enough to participate in multidisciplinary therapy, which is approximately 10% of the total stroke population (Revalidatie Nederland, 2012). In Chapter 2, 3, 4 and 8, we intentionally aimed to include a heterogenous sample of patients with ABI to increase its representativeness. A general concern might regard a potential selection bias, where patients who are willing to participate are probably patients who are less impaired (Knudsen, Hotopf, Skogen, Øverland, & Mykletun, 2010; Olson, Parkinson, & McKenzie, 2010). Indeed, our patient samples were relatively young with mild to moderate cognitive impairments, which might be considered as a limitation since we cannot generalise the findings to an older sample with more severe cognitive impairments. On the other hand, including patients with mild cognitive impairment might also be considered a strength, as developing more sensitive measures is crucial in this group.

With regard to patients with TBI, clinicians may use several measures to diagnose and classify the severity of the injury, such as the Glasgow Coma Scale (GCS), duration of loss of consciousness or duration of post-traumatic amnesia. Classification of mild TBI is primarily based on an initial GCS score of 13–15 (Kay et al., 1993). However, because a majority of mild TBI patients are not admitted to hospitals, these clinical measures are often not available. In these cases, a patient's story is the leading factor to diagnose mild TBI. Neuroimaging (CT or MRI) is additionally used to assess brain abnormalities. However, CT or MRI do not show traumatic abnormalities for the majority of TBI patients (van der Horn et al., 2020). This was also the case in our sample of patients with TBI, where half of the sample did not show abnormalities on a brain scan. Diffusion tensor imaging (DTI) has been used in patients to study axonal damage that may be the underlying cause of symptoms following mild TBI (Khong, Odenwald, Hashim, & Cusimano, 2016). DTI is not used in routine clinical practice yet. However, some have urged caution in the interpretation of DTI at the individual level (Wintermark et al., 2015). Developing sensitive behavioural measures to assess cognitive consequences of mild TBI seems therefore even more relevant.

Future research

Development of outcome measures

This dissertation addresses the tip of the iceberg and further refinement is clearly needed. Digital tests allow for the development of novel outcome measures providing more detailed information about underlying cognitive processes (Diaz-Orueta, Blanco-Campal, Lamar, Libon, & Burke, 2020; Fellows, Dahmen, Cook, & Schmitter-Edgecombe, 2017; Parsey & Schmitter-Edgecombe, 2013). For instance, embedded measures of response time have been used to assess constructs of processing speed (Guevara, Rizo, Ruiz-Díaz, & Hernández-González, 2009; Libon et al., 2014). Algorithms have supported the evaluation of the process of construction in drawing tests (Davis, Libon, Au, Pitman, & Penney, 2014; Kim, Cho, & Do, 2010; Müller, Preische, Heymann, Elbing, & Laske, 2017). Digital versions of cancellation tests have enabled to detect disorders in spatial exploration, like disorganized search (Ten Brink, van der Stigchel, Visser-Meily, & Nijboer, 2016). Hence, numerous outcome measures can be incorporated in a d-NPA, which allow for the exploration of cognitive processes that might not be objectified with paper-and-pencil tests.

VR-simulations allow for extensive possibilities in terms of outcome measures as well, such as analyses of errors, navigational measures, and eye-tracking measures, (Lutz et al., 2017; Parsey & Schmitter-Edgecombe, 2013). Eye-tracking enables clinicians to evaluate search patterns by analysing visual fixations on the left or right side of space. A study of Kortman & Nicholls

(2016) showed that eye-tracking was a successful method to differentiate between patients with and without visuo-spatial neglect. Eye-tracking in immersive VR is a relatively new development, which opens new possibilities for conducting research concerning perception and attention in simulated daily life situations (Clay, König, & König, 2019). Furthermore, VR enables researchers to investigate navigational patterns including travelled distance and the number of stops, pauses, and intersections. Intersections indicate the amount of crossings with one's own path, where a higher number of intersections reflects a less organized pattern (see Figure 9.2 for the application in a VR-based task). A combination of outcome measures, may be used to identify distinct pattern of scores discriminating patients from cognitive impairment and healthy participants. In a large sample, data-driven machine learning analyses might reveal which patterns of scores occur from the data. Specific patterns might identify a certain clinical population. Data-driven analyses may enable a shift towards developing more sophisticated models of behaviour.

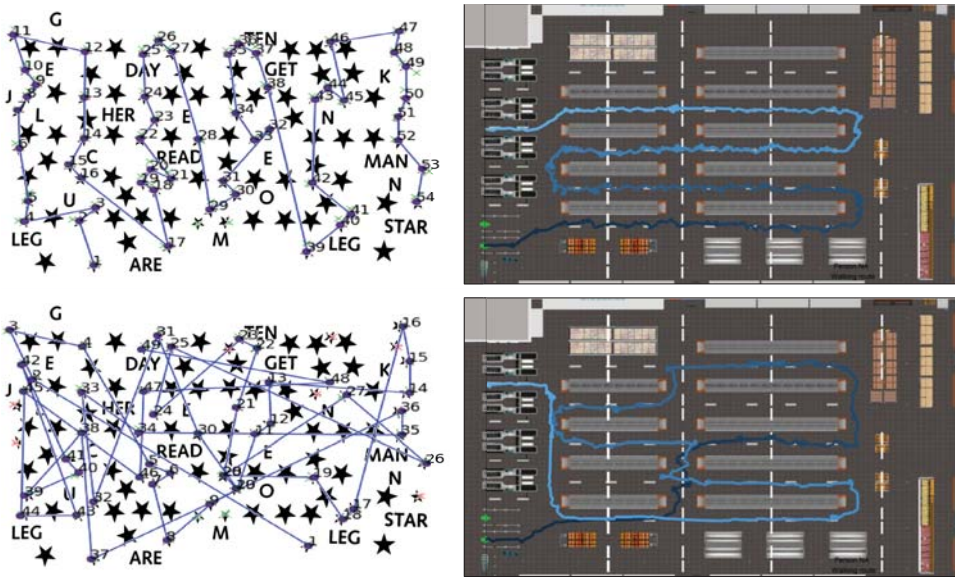

Figure 9.2. Intersections have been used to study disorganized search on the Star Cancellation test in patients with visuospatial neglect (Ten Brink et al., 2016). The order of cancellations represents a search pattern. In the upper figure, there are no intersections as the patient cancelled the targets in a vertical direction. The number of intersections is higher in the lower figure, representing disorganized search. An intersection rate could also be applied on a VR-based grocery task. The right figures are maps of the virtual supermarket. The blue lines represent the pattern of a patient's chosen route through the supermarket. In the upper figure there are no intersections, whereas there are several intersections in the lower figure.

Validity and reliability

Development of assessment tools entails the establishment of evidence regarding feasibility, reliability, and validity. The CoCo-P inventory is appropriate to capture cognitive complaints in daily life in patients with mild ABI. The fact that the CoCo-P was considered representative for patient's difficulties (face validity) makes it a valuable tool. Its construct validity should be addressed by estimating its association with other measures of the same construct (e.g., Checklist for Emotional and Cognitive Consequences). We concluded that d-NPA and VR-based tasks are both highly feasible in patients with ABI. In order to establish convergent validity (as part of construct validity), digital tests must possess moderate to strong correlations with the paper-and-pencil tests as "gold standard". Investigating the convergent validity of VR-based tasks seems a bigger challenge. A previous meta-analysis has investigated the relation between performances on a VR-based tasks with performances on neuropsychological tests and found only moderate correlations (Negut et al., 2016). This result may be explained by the fact that VR-based tasks are more demanding then neuropsychological tests. Moreover, studies have investigated the relation between performances on VR-based tasks and performances in real-life (Buxbaum, Dawson, & Linsley, 2012; Claessen, Visser-Meily, De Rooij, Postma, & Van Der Ham, 2016). For instance, a recent study showed that the cognitive load (the load that imposes on an individual's cognitive system) during navigation within a virtual environment was no different than within a real-life environment (Armougum, Orriols, Gaston-Bellegarde, Marle, & Piolino, 2019). Hence, investigating the relation between performances on VR-based tasks and performances in real-life seems informative, yet not all measures in VR are available in real-life tasks (e.g., eye-fixations).

Clinical norms

Clinical norms are needed, as norms are the key to interpret test performances. Clinical norms must be updated regularly at a frequency that maps onto the speed of technology development (Germine, Reinecke, & Chaytor, 2019). Ideally, clinicians and researchers should select hardware and software with desirable technological properties and preferably agree on one open source software (Germine et al., 2019). Which parties (e.g., professional associations, commercial test developers) would maintain digital tests and clinical norms still require some thoughts, as this problem has not been solved yet.

Treatment

Computer-based and VR-based training have been found promising in improving cognitive function (Bogdanova, Yee, Ho, & Cicerone, 2016; Coyle, Traynor, & Solowij, 2015; Larson, Feigon, Gagliardo, & Dvorkin, 2014; Laver, George, Thomas, Deutsch, & Crotty, 2015; Maggio

et al., 2019). However, few studies have investigated whether training effects transfer to real-world performances (van Heugten, Ponds, & Kessels, 2016). Furthermore, VR-based training may not only be applied to improve cognitive function, but may also offer the possibility to train skills and compensation strategies (Gamito et al., 2017; van der Kuil, Visser-Meily, Evers, & van der Ham, 2018). Environmental interaction is crucial to train specific skills or to master compensation strategies and VR may provide a safe environment to do so (Rose et al., 2005). However, there is little evidence supporting the generalisation of training effect to real-world performances. Future research needs to improve study designs by including larger samples, longitudinal designs, and a greater range of outcome measures (including functional and participation measures) to assess the wider effect of technology-based cognitive training.

Embracing technology: the perspectives of clinicians and researchers

There is no doubt that the field of neuropsychology is going to move progressively towards the implementation of technology (Bilder, 2011). Development of technology can move forward rapidly if we embrace technology. Some express fear that technology will somehow replace clinicians. However, technology is just a tool enabling a more standardized administration and detailed data collection, and proper use can outperform a human examiner in precision (Bilder, 2011). Technology in the field of neuropsychology may influence several clinicians in clinical practice, such as physicians and occupational therapists, as well as researchers in behavioural research. It would be informative to inquire clinicians' and researchers' perceptions about how their roles and work might change as these technologies become more widespread. I asked several clinicians and researchers to respond.

Neuropsychologists in clinical practice

Benefits include the few materials that are needed during a d-NPA, as opposed to many materials that are needed during a paper-and-pencil assessment (e.g., booklets). Another benefit involves automatic scoring, which means that test results can be available shortly after the administration, saving valuable professional time. It is important to note that behavioural observations remain crucial to interpret the findings. Tests that allow self-administration are not preferred as behavioural observations would be lost. It is possible that the lack of exposure to technology and the comfort with paper-and-pencil tests (on which neuropsychologists were initially trained), contributes to the lack of utilization of technology in clinical practice. Instruction manuals may not be sufficient for neuropsychologists to feel at ease with a new technology, so training programs would be required.

Neuropsychologists in research

In the field of behavioural or cognitive neuroscience, numerous computerized experimental tasks are developed to unravel cognitive processes. Outcome measures can be computed beforehand, but also afterwards which creates extensive possibilities. However, with computerized tasks participants remain well aware of the laboratory setting, preventing researchers to provoke real-life behaviour. With VR, participants are immersed in a virtual environment resulting in a sense of presence described as "really being in a virtual environment". More natural behaviour can be provoked and unique research questions can be answered. Promising development is taking place regarding a better resolution and improved perception. Just as important is the promising development regarding the collection of reliable data and the use of modern data analytics (e.g., machine learning). Data are of no use if we cannot extract useful knowledge from them and collaborations with data scientists play a crucial role here.

Rehabilitation physicians

Neuropsychological assessment is the first step in cognitive rehabilitation. It is relevant to consider the benefits of d-NPA in terms of time and costs (e.g., automatic scoring, fewer test materials). Translating well-known paper-and-pencil tests into digital tests is preferred, so clinicians are already familiar with these tests and underlying cognitive constructs. More outcome measures may be a strength as more information is available, yet not all outcome measures might be relevant with regard to certain referral questions. It might, therefore, be increasingly important to keep the referral question in mind when analysing the findings. With regard to VR, it should be clear among clinicians which referral questions can be answered based on the results, and subsequently how the results can be used in treatment decisions.

Occupational therapists

Neuropsychological assessment is crucial to formulate goals in occupational therapy. VR-simulations might be of great value to administer a functional assessment in an interactive and dynamic environment, especially when an assessment in real-life is not feasible. VR-based tasks might be an important improvement for patients as it would lead to a better understanding regarding their cognitive difficulties. More information would be available to formulate goals in terms of cognitive domains and specific triggers hampering everyday performance (e.g., distracting stimuli, fatigue). Also, VR-simulations seem ideally to be used in occupational therapy to teach patients compensation strategies in a safe and easily accessible environment. It is, nowadays, time consuming to take patients outside to practice compensation strategies (e.g., crossing the street safely, grocery shopping). VR allows for a

recording to be reviewed at any point during the therapy session. Exercises may be paused, which allows therapists to provide immediate feedback. In order to use VR-simulations in clinical practice, the technology should be easy to use for both therapist and patient.

What is needed for this technology to be implemented into clinical practice?

In the coming years, several steps should be undertaken to embrace technology in the future of the neuropsychological field. I describe five steps that are needed, though not necessarily in this order, to implement technology into clinical practice.

- An important step is the refinement of the assessment and training tools and the establishment of evidence regarding reliability and validity. A close collaboration between clinicians, researchers and commercial developers is important here. Together they should select hardware and software with desirable technological properties and preferably agree on one open source software. Commercial developers play a crucial role in the sustainability of the instruments by managing updates of software, hardware, and licenses.
- Clinical norms must be developed and updated regularly at a frequency that maps onto the speed of technology development. Ideally, each institution should use the same clinical norms to achieve uniformization. To do so, possibilities need to be explored regarding parties that have the resources to manage clinical norms (e.g., commercial developers, professional associations).
- Technology should be embraced in the training of students (e.g., neuropsychologists, occupational therapists), and training programs are required for working clinicians to feel at ease with the technology.
- Clinicians should experiment with the new tools and involve patients in the process. Using knowledge derived from patient experience will give insight into possible implementation barriers. Collaborating with patients can lead to potential solutions that clinicians would possibly not think of.
- Finally, clinicians and researchers should involve healthcare managers in the process, as managers must also be prepared to lead their staff through the change. They need to be included to understand its impact on workflows and the beneficial implications for patient care. They can then help to structure the implementation process and address contextual barriers.

As in many areas, we envision the future of neuropsychology will be digital. The need to move beyond the sole use of paper-and-pencil tests is palpable among clinicians, but more

work is needed to refine our tools before it may be used in clinical practice. This dissertation describes the first steps, but we are moving forward in assessing, understanding and treating cognitive difficulties patients encounter in daily life.

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Summary

Neuropsychology from paper-and-pencil to technology

Advancing cognitive rehabilitation

Neuropsychology is dedicated to understand the relation between the brain and neuropsychological functions, including emotion, behaviour and cognition. Cognition is an overall term for several different functions by which an individual acquires, processes, stores and acts on information from the environment. Cognition is typically conceptualized in terms of domains of functioning, such as memory, attention, and executive functioning. Clinical neuropsychologists are consulted whenever there are symptoms involving cognition. For instance, when patients experience difficulties regarding memory or attention.

Acquired Brain Injury (ABI) is defined as brain damage that occurs after birth, and is caused by either traumatic brain injury (e.g., head trauma due to traffic accidents, assaults) or nontraumatic injury (e.g., ischemic or haemorrhagic stroke, brain tumours). Depending on the location and severity of the brain injury, ABI can result in physical, social, emotional, behavioural and cognitive impairment, and outcome can range from complete recovery to permanent disability. Cognitive impairment can be one of the most devastating consequences of a brain injury, as it may interfere with activities of daily living (e.g., eating, bathing, getting dressed), relationships, leisure and work. Cognitive rehabilitation starts with a thorough neuropsychological assessment, which consist of a clinical interview to gather relevant information, neuropsychological testing, analysis and integration of findings, and feedback to the patient. The conclusions of the assessment are used to formulate an appropriate treatment plan.

The general objective of this dissertation was to investigate the use and added value of novel instruments in cognitive rehabilitation for patients with ABI. To achieve this objective, we formulated three aims: (1) to develop an instrument to systematically assess cognitive complaints in daily life; (2) to investigate the use of a digital version of existing tests to measure cognitive function, and to capitalize the opportunities afforded by digital tests by developing novel outcome measures; (3) to investigate the use and added value of advanced technology to assess cognitive function in a more sensitive and dynamic manner, and to inventory the use of advanced technology to improve cognitive function.

Part 1: Paper-and-pencil

A clinical interview is conducted to require information from the patient and relative (or significant other. An important aspect is the inventory of the cognitive complaints. To date, however, there is little uniformity and standardization in the assessment of cognitive complaints. This leads to the possibility that some complaints are missed, or that an increase or improvement of complaints remain unnoticed. In **Chapter 2**, the *Cognitive*

Complaints - Participation (CoCo-P) inventory was developed as a patient- and relative-reported measure to assess cognitive complaints based on available literature, expert meetings, semi-structured interviews with patients, and a quantitative study. We found that the CoCo-P seemed appropriate to differentiate between cognitively healthy controls (n = 102) and patients experiencing cognitive complaints during daily life activities (n = 46). The majority of patients (87–96%) experienced cognitive complaints, mostly related to attention, at work/education, during leisure activities, and in contact with family/friends and community. Patients reported a higher level of fatigue following each daily life activity, compared to healthy controls. Patients reported more complaints than their relatives. Patients might have underestimated their functioning (and therefore reported more complaints) or relatives might have overestimated a patient's functioning (and therefore reported fewer complaints). As cognitive complaints negatively affect rehabilitation goals, such as functional independence and participation in society, it is of great importance to assess cognitive complaints in a standardized manner.

Part 2: Digital neuropsychological tests

A neuropsychological test battery mostly consists of paper-and-pencil tests, with each test targeting a specific cognitive domain. A digital neuropsychological assessment (d-NPA) has important benefits compared to a paper-and-pencil NPA, such as a more standardized administration and an automatized scoring. Notwithstanding the benefits, the question rises whether a d-NPA is feasible in patients with ABI, as bright screens may cause sensory overload within these patients. In **Chapter 3**, we investigated the feasibility and user-experience in stroke patients (n = 59), traumatic brain injury patients (n = 61) and healthy controls (n = 159). Overall, 94% of patients completed the d-NPA, and the digital administration was considered pleasant by patients and healthy controls. Conventional norms that exist for paper-and-pencil tests were not applicable on the digital version of the tests, as up to 34% of healthy controls showed an abnormal performance on half of the tests. Developing and regularly updating clinical norms is crucial in neuropsychological assessment and should be taken into account in order to implement a d-NPA in clinical practice. People who were more experienced with working with a tablet did not perform better on digital tests. Hence, tablet familiarity did not affect test performance, which is particularly important in neuropsychological assessment.

Furthermore, digital tests offer the possibility to obtain more information inaccessible by paper-and-pencil tests. A next step was the development of additional outcome measures that go beyond the conventional outcome measures of paper-and-pencil tests. Performances

on paper-and-pencil tests are usually scored by examining a final score, such as the total duration, number of correct responses, or a final drawing. Digital tests allow for a highly detailed registration and evaluation, which provides insight into "how" a patient attained a final outcome. In **Chapter 4**, we assessed performance stability by evaluating the number of fluctuations in test performance on three well-known tests, namely the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT) and the Stroop Colour and Word Test (Stroop). Patients with ABI (n = 91) fluctuated more in their performance on the RAVLT, TMT and Stroop, when compared to healthy controls (n = 161). Furthermore, 4–15% of patients who performed inside normal range on the conventional final scores, performed outside normal range on the performance stability measures. This might be considered as an important clinically relevant finding as we were able to objectify cognitive impairment among those patients, which would not have been objectified with paper-and-pencil tests. The performance stability measures, nor the conventional final scores, were associated with cognitive complaints in daily life. An explanation might be that performances on neuropsychological tests do not correspond with daily life performances.

Part 3: Advanced technology

Test results on paper-and-pencil tests do not translate easily to daily life, which refers to a lack of ecological validity. This is probably due to the fact that neuropsychological tests are administered under optimal condition in a quiet and non-distracting room. In daily life, however, patients are required to perform cognitive tasks under challenging and dynamic conditions. A high ecological validity of neuropsychological tests is important since the recommendations based on the test results may have significant consequences for the lives of patients and their relatives. Complementary tests have been developed, such as observational scales or ecologically valid tests conducted in the real-world. Virtual Reality (VR) has been used to assess how patients would perform in daily life situations. With VR, tests may be developed without losing control over stimulus presentation, distractions and complexity. In **Chapter 5**, we administered static tests (i.e., paper-and-pencil tests) and dynamic tests (i.e., observational scale, ecologically valid test and VR-based task) in patient with visuo-spatial neglect. Visuo-spatial neglect is a frequent and disabling disorder in lateralized attention. Patients with visuo-spatial neglect fail to attend stimuli presented at the contralesional side of space. These patients manifest symptoms such as bumping into doorframes, eating food from only one side of their plate, and ignoring people who are located at their contralesional side. In our study, the underlying factor structure corresponded to our proposed conceptual distinction between static tests and dynamic tests. Moreover, patients who showed neglect

on tests within the dynamic cluster had poorer motor functions than patients who showed neglect on tests within static cluster. Dynamic tests require more from motor functions, especially when they are impaired. Since the attention capacity is limited, this will likely compromise the simultaneous execution of a different task (e.g., detecting targets). In **Chapter 6**, we investigate the added value of a non-immersive VR-based task to asses visuo-spatial neglect. The VR-based task consisted of a simulated driving task where patients were instructed to drive at the center of the right lane. Participants needed to adjust their position continuously as "side wind" was simulated. Patients with left-sided neglect deviated more to the left, compared to patients without neglect. Interestingly, patients who showed "recovered" neglect on traditional tests, also deviated more to the left. The deviation was larger in patients with more severe neglect. An extra 6–30% of patients who did not show neglect on a paper-and-pencil test nor on an observational scale, did show neglect behavior on a simple 2-minute simulated driving task.

In **Chapter 7**, we investigated the feasibility of VR in stroke patients who were referred for inpatients or outpatient rehabilitation care. In this study, we used two primary user interfaces, namely non-immersive VR by using a computer monitor (CM) and immersive VR by using a head-mounted display (HMD). Although the use of VR in neuropsychological assessment has been promising, is it feasible to use in stroke patients? How do stroke patients experience non-immersive and immersive VR? Both user interfaces were feasible to use in stroke patients, irrespective of clinical referral (in- or outpatient rehabilitation care). Patients reported an enhanced feeling of engagement, transportation, flow, and presence, but more negative side effects when tested with a HMD, compared to a CM. Negative effects are likely to decrease with more sophisticated HMD, which is a lead focus in best practice guides for VR development. The majority of stroke patients had no preference for one user interface over the other, yet younger patients tended to prefer a HMD. VR seems highly feasible in stroke patients. A next step would be to investigate the usability of VR in neuropsychological assessment.

Current understanding of neuroplasticity has led to novel insights in treatment by applying a remediation approach. Neuroplasticity is the ability of the brain to create, strengthen, and modify neurological connections. A wide range of treatments are developed based on the principles of neuroplasticity and are directed to restore or retrain cognitive function. In **Chapter 8**, we provided an overview of studies regarding the most discussed treatments targeting memory impairment following ABI, namely VR-based interventions, computerized-based cognitive retraining and non-invasive brain stimulation. A systematic literature search was completed and three studies were found describing VR-based interventions, seven studies describing computerized-based cognitive retraining, and 5 studies describing non-

invasive brain stimulation. Computerized-based cognitive retraining was considered the most promising novel approach of the last decade. VR-based interventions also showed promising results. However, the number of studies regarding VR-based interventions were limited and the methodological quality low. Studies representing non-invasive brain stimulation did not find evidence in improving memory function. Even though computerized-based cognitive retraining and VR-based training showed great promises, more research is needed in order to implement these approaches in clinical practice.

Finally, although this dissertation may address the tip of the iceberg, it reveals promising areas for further refinement. In **Chapter 9**, I integrate the findings of the individual studies, address methodological considerations, and formulate recommendations for future research and clinical practice.

The ICF (International Classification of Functioning) can create a common language that enable us to form a holistic view of a patient, which seems crucial when assessing cognitive functioning. The ICF distinguishes three levels: body function and structure (i.e., impairments due to loss in function as measured by neuropsychological tests); activities (i.e., functional limitations as measured with VR-based tests) and participation (i.e., restrictions that limits the fulfilment of a role in society as measured with self-report questionnaires). When applied to cognition, impairments (e.g., memory impairment) may lead to limitations (e.g., difficulties remembering past conversations), and these limitations may lead to restrictions (e.g. not being able to work). Our assessment tools may function as an example of how cognitive functioning can be assessed on these three levels of functioning. Furthermore, neuropsychological assessment has been increasing in various clinical populations where mild cognitive impairment continues to be under recognised. A more holistic approach to assess cognitive functioning may further improve the care of these patients.

Future research should focus on the extensive possibilities in terms of outcomes measures that digital tests and VR-based tasks allow. Development of assessment tools also entails the establishment of evidence regarding feasibility, reliability, and validity. Clinical norms are needed, as norms are the key to interpret test performances. Furthermore, future research needs to improve study designs by including larger samples, longitudinal designs, and a greater range of measures (including functional and participation measures) to assess the wider effect of technology-based cognitive training.

Technology in the field of neuropsychology may influence several clinicians in clinical practice, such as physicians and occupational therapists, as well as researchers in behavioural research. I collected several clinicians' and researchers' perceptions about how their roles and work might change as these technologies become more widespread. Finally, I

describe several steps that should be undertaken to embrace technology in the future of the neuropsychological field.

Cognitive consequences can be one of the most devastating consequences of brain injury, as it generally interferes with all aspects of daily life. Neuropsychological assessment is crucial to assess cognitive strengths and weaknesses, and also to formulate an appropriate treatment plan. As in many areas, we envision the future of neuropsychology will be digital. The need to move beyond the sole use of paper-and-pencil tests is palpable among clinicians, but more work is needed to refine our tools before it may be used clinical practice. This dissertation describes the first steps, but we are moving forward in assessing, understanding and treating cognitive impairment.

Het verhaal van Tamara

Op 21 december 2015 werd ik opgetild waardoor ik mijn hoofd tegen een paal stootte en op de grond viel. Ik hoorde anderen roepen: “Dat was bijna raak!”, maar het was raak. De volgende ochtend had ik niet gelijk door hoe ik eraan toe was. Gedurende die dag merkte ik dat ik niet wakker kon blijven. Ik ben naar de huisarts gegaan die mij adviseerde om rustig aan te doen.

De eerste weken had ik last van hoofdpijn en extreme vermoeidheid, waardoor ik het overgrote deel van de dag sliep. Ik was vergeetachtig, kon me moeilijk concentreren en had veel last van prikkels, zoals fel licht en geluid. Ik moest inleveren op mijn sociale leven. Sporten, een concert- of bioscoopbezoek lukte niet meer. In april 2016 probeerde ik mijn werk weer een paar uur per dag op te pakken. Dit ging erg moeizaam. Ik kon niet lang achter een computer zitten, mijn aandacht niet goed bij mijn werk houden en in contact met klanten liet mijn geheugen mij regelmatig in de steek. Desalniettemin kreeg ik meer verantwoordelijkheden. Mijn klachten werden erger, maar ik had moeite te accepteren dat ik het niet volhield om te functioneren als voorheen.

Op 20 juli 2016 ben ik door de huisarts doorverwezen naar een neuroloog en een revalidatiearts. Zij gaven woorden aan wat ik meemaakte: de klachten pasten bij niet-aangeboren hersenletsel (NAH). Zij adviseerden mij om tijdelijk te stoppen met werken om rust en tijd te nemen voor de behandeling. Ik kreeg een neuropsychologisch onderzoek waar mijn denkfuncties getest werden met pen-en-papier tests. Het koste me veel moeite de tests te voltooien, maar er kwamen slechts enkele subtiele tekorten naar voren. Wat een opluchting zou moeten zijn, was eerder frustrerend omdat ik geen erkenning ervoer voor wat ik doormaakte. Ook had deze uitslag later nog gevolgen. Omdat er geen duidelijke stoornissen naar voren kwamen uit het onderzoek, was de bedrijfsarts bijvoorbeeld niet direct bereid om mij de nodige voorzieningen toe te kennen voor een rustige start die de revalidatiearts mij had aanbevolen.

Het is nu 5 jaar later en het herstel ging met vallen en opstaan. In de afgelopen jaren hebben verschillende mensen met NAH contact met mij opgenomen die ook met onbegrip te maken kregen. Er valt nog veel winst te behalen voor patiënten met NAH wat betreft de diagnostiek, begeleiding en behandeling.

Nederlandse samenvatting

Van pen-en-papier naar technologie
Bekijk het door een andere bril

Tamara's verhaal is een voorbeeld van talloze verhalen, waar hersenletsel zorgt voor een breuk in de levenslijn. Alles wordt van de ene op de andere dag heel anders. NAH is de meest voorkomende diagnose in de revalidatiegeneeskunde in Nederland. Bij patiënten met NAH is er na de geboorte schade in de hersenen opgetreden. Deze hersenbeschadiging kan door een interne oorzaak ontstaan, zoals een beroerte (hersenbloeding of herseninfarct), ruimte-innemende processen (tumoren), infecties (hersenvliesontsteking), of door een externe oorzaak zoals een traumatisch hersenletsel (een klap krijgen op het hoofd door een val of botsing). Jaarlijks worden er in Nederland 40.000 patiënten met een beroerte en 20.000 patiënten met een traumatisch hersenletsel opgenomen in het ziekenhuis, de twee meest voorkomende oorzaken van NAH. Naast de zichtbare lichamelijke gevolgen (zoals een halfzijdige verlamming) heeft NAH ook niet-lichamelijke gevolgen, zoals problemen in de cognitie. Cognitie is een paraplubegrip voor verschillende denkfuncties, zoals het geheugen, de aandacht, en de taal.

Neuropsychologie houdt zich bezig met de relatie tussen hersenen en gedrag, emotie en cognitie. Neuropsychologen zijn betrokken bij de diagnostiek en behandeling van kinderen en volwassenen met neurologische of psychiatrische aandoeningen. Neuropsychologen worden geraadpleegd als een patiënt cognitieve klachten rapporteert, zoals vergeetachtigheid of concentratieproblemen. Cognitieve problemen hebben vaak een negatieve uitwerking op alle levensgebieden, zoals thuis, werk, vrijetijdsbesteding of sociale gelegenheden. Wanneer patiënten vastlopen in het dagelijks leven worden ze doorverwezen voor *cognitieve revalidatie*. Dit revalidatietraject begint met de diagnostiek om in kaart te brengen welke cognitieve functies aangedaan zijn door het letsel. Hiervoor wordt een neuropsychologisch onderzoek ingezet, dat bestaat uit een anamnese (gesprek met patiënt en een naaste) en een testonderzoek. Op basis van de testresultaten wordt een behandelplan gemaakt.

Deel 1: Cognitieve klachten: de ervaring van een patiënt en zijn naaste

De eerste stap in de diagnostiek is het gesprek met een patiënt en een naaste (partner, familielid, vriend): de anamnese. Het belangrijkste doel van de anamnese is informatie verkrijgen over het beloop, de ernst en de gevolgen van de klachten in het dagelijks leven. Naast het verhaal van de patiënt, wordt ook het verhaal van een naaste meegenomen. De verhalen van de patiënt en een naaste komen niet altijd overeen. Dit kan erop wijzen dat de patiënt en zijn naaste een andere beleving hebben van de klachten. Informatie inwinnen van zowel de patiënt als een naaste is daarom belangrijk. Ter ondersteuning van het gesprek kunnen vragenlijsten ingezet worden. De huidige vragenlijsten maken echter geen gebruik

van dagelijkse voorbeelden. Vragen zoals "Heeft u problemen in de aandacht?" zijn voor patiënten vaak moeilijk te beantwoorden. Het gebruik van een dagelijkse situatie kan een patiënt helpen, zoals "Lukt het u om uw aandacht bij uw werk te houden, zonder afgeleid te worden door dingen die om u heen gebeuren?". Op deze manier krijgt men ook inzicht in de levensgebieden, waarin een patiënt zich gehinderd voelt (zoals werk of autorijden). In **hoofdstuk 2** beschreven we de ontwikkeling van een vragenlijst gericht op cognitieve klachten in het dagelijks leven. Wij hebben de *Cognitive Complaints – Participation* (CoCo-P) vragenlijst ontwikkeld op basis van literatuuronderzoek, interviews met patiënten en bijeenkomsten met behandelaars, psychologen, revalidatieartsen en cognitiewetenschappers. De vragenlijst werd voorgelegd aan 46 patiënten met NAH, 33 naasten en 102 gezonde participanten. Patiënten rapporteerden de meeste cognitieve klachten tijdens werk of opleiding, vrijetijdsbesteding en in het contact met vrienden, familie en omgeving. Gezonde participanten rapporteerden heel weinig klachten. De rapportages van patiënten en naasten over het klachtenniveau van de patiënt bleken niet altijd overeen te komen. Patiënten rapporteerden meer klachten dan hun naasten. Deze bevinding weerspiegelt mogelijk dat patiënten hun eigen functioneren onderschatten (en dus meer klachten rapporteren) of dat naasten het functioneren van de patiënt overschatten (en dus minder klachten rapporteren). Patiënten kunnen een verminderd inzicht hebben in hun eigen kunnen. Tevens kan het voor een ander, zelfs voor een naaste, moeilijk zijn om cognitieve klachten te observeren. De CoCo-P bleek een veelbelovend instrument om cognitieve klachten op een systematische wijze in kaart te brengen. Met het toevoegen van een vragenlijst aan een anamnese kan men voorkomen dat klachten worden gemist.

Deel 2: Digitale neuropsychologische tests: het meten van cognitieve functies

Wanneer de anamnese is afgerond, wordt het neuropsychologisch testonderzoek ingezet om de cognitieve functies van een patiënt te testen. Het testonderzoek bestaat uit verschillende pen-en-papier tests die specifieke cognitieve functies in kaart brengen. Patiënten worden bijvoorbeeld gevraagd een lijst met woorden te onthouden of een complexe figuur na te tekenen. Het testonderzoek wordt doorgaans afgenomen in een rustige kamer, met zo min mogelijk afleiding uit de omgeving. Deze statische testsituatie maakt dat er een optimale prestatie kan worden geleverd door de patiënt. De prestaties van een patiënt worden beoordeeld door te kijken naar het aantal correcte antwoorden of naar de tijd die een patiënt nodig had om een test te voltooien. De prestaties worden afgezet tegen de prestaties van een normgroep (een grote groep gezonde mensen van hetzelfde geslacht, leeftijd en

opleidingsniveau). Op deze manier kan een neuropsycholoog beoordelen of een prestatie van een patiënt gelijk, beter of slechter is dan de normgroep. Aan de hand van de resultaten en de observaties van de neuropsycholoog wordt een cognitief profiel gevormd van de functies die zijn aangedaan en de functies die relatief gespaard zijn gebleven.

Zoals het verhaal van Tamara laat zien, zijn pen-en-papier tests soms niet gevoelig genoeg om milde cognitieve problemen te vangen. Het belangrijkste voordeel van digitale tests is dat de prestatie van een patiënt van A tot Z wordt vastgelegd. Neuropsychologen hebben naast een eindscore (zoals het aantal correcte antwoorden of de totale tijd) meer informatie om de prestatie te beoordelen. Een digitaal testonderzoek is ontwikkeld door Philips Research, waar een patiënt tests krijgt aangeboden op een tabletcomputer en gebruik maakt van een digitale pen (Figuur 1). Zoals Tamara in haar verhaal vertelt, kunnen patiënten met NAH overgevoelig zijn voor fel licht wat het werken met een computer bemoeilijkt. In **hoofdstuk 3** onderzochten we of het haalbaar is om een compleet digitaal testonderzoek af te nemen bij 59 patiënten die een beroerte hebben doorgemaakt, 61 patiënten met een traumatisch hersenletsel en 159 gezonde participanten. Zowel patiënten als gezonde participanten hadden het digitale testonderzoek afgemaakt en als aangenaam ervaren. Tevens ontdekten we dat de normen die ontwikkeld zijn voor de pen-en-papier tests niet zomaar bruikbaar

Figuur 1. Een digitaal testonderzoek bestaande uit verschillende digitale tests die cognitieve functies in kaart brengen.

zijn voor digitale tests. Het scherm van de tabletcomputer is bijvoorbeeld gladder, waardoor patiënten slordiger tekenen dan op papier. Tenslotte ontdekten we dat participanten die meer ervaring hadden met een tabletcomputer niet beter presteerden op de digitale tests. Dit is een belangrijke bevinding, omdat de wijze van afname (pen-en-papier of digitaal) geen invloed mag hebben op de prestatie van een patiënt.

In **hoofdstuk 4** hebben wij een maat ontwikkeld om de stabiliteit van een prestatie te beoordelen. Patiënten met NAH kunnen bijvoorbeeld een snelle start maken, maar de snelheid niet volhouden tot het einde van de test, terwijl gezonde participanten dat wel kunnen. Tot nu toe werd dit met het blote oog geobserveerd door een neuropsycholoog. Observaties zijn echter een subjectieve maat, waardoor de beoordelingen tussen neuropsychologen kunnen verschillen. Bij drie digitale tests hebben we een maat ontwikkeld die de stabiliteit van de prestatie kan objectiveren aan de hand van een score. Op deze manier hebben neuropsychologen niet alleen de eindscore, maar ook een score over *hoe* een patiënt tot die eindscore is gekomen. Het bleek dat patiënten met NAH een minder stabiele prestatie hadden dan gezonde participanten. Tevens had 4–15% van de patiënten een 'goede' eindscore, maar een instabiele prestatie.

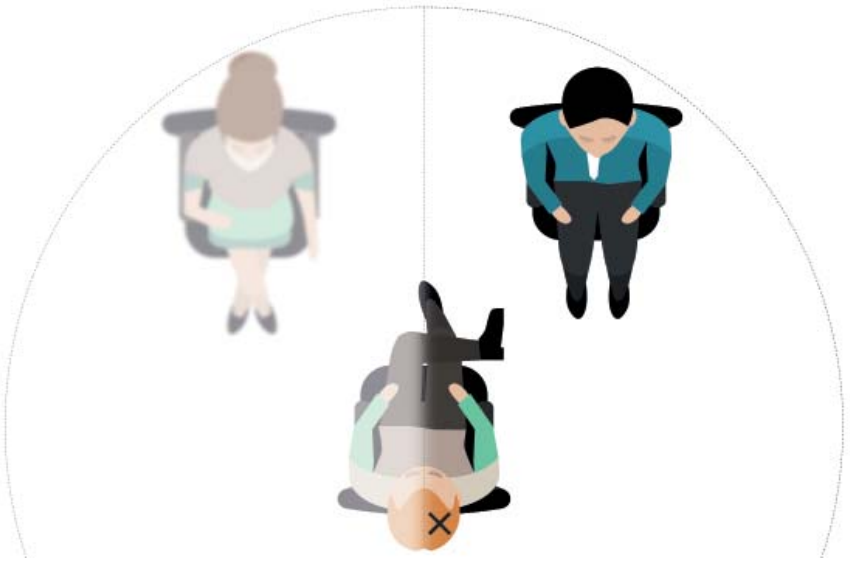
Deel 3: Geavanceerde technologie: interactie met de omgeving!

Aan neuropsychologen wordt gevraagd om uitspraken te doen over het dagelijks functioneren van de patiënt. In veel gevallen wordt dit gebaseerd op het cognitief profiel dat verkregen is met neuropsychologische pen-en-papier tests. Deze statische tests komen echter niet overeen met de dynamiek van het dagelijks leven. Neuropsychologische tests (zowel pen-en-papier als digitaal) worden afgenomen in een rustige kamer, met zo min mogelijk afleiding. In het dagelijks leven moet men echter presteren in een drukke omgeving, zoals een open werktuin. Om cognitieve functies in een dagelijkse situatie in kaart te kunnen brengen zijn dynamische tests ontwikkeld, zoals observatieschalen en ecologisch-valide dubbeltaken. Ecologisch-valide dubbeltaken zijn taken die in een dagelijkse situatie afgenomen worden, zoals de Multiple Errands Test (een planningstaak in een winkelcentrum) of de Mobility Assessment Course (een zoektaak in een gang). Een nadeel van dit soort taken is dat ze worden uitgevoerd in een omgeving die niet volledig te controleren is. Het kan op het ene moment heel rustig zijn in een winkelcentrum en op het andere moment heel druk. In een dagelijkse situatie kan men geen prikkels toevoegen of wegnemen om te kijken wat voor invloed dit heeft op een patiënt. De huidige technologische ontwikkelingen op het gebied van Virtual Reality (VR) kunnen uitkomst bieden. VR biedt de mogelijkheid mensen te testen in een virtuele omgeving die het dagelijks leven nabootst, zoals een virtuele supermarkt. Er is

volledige controle over de virtuele omgeving, waardoor geluiden, producten en winkelende mensen kunnen worden toegevoegd of verwijderd. Elke handeling van een patiënt wordt geregistreerd, waardoor de invloed van de prikkels op het gedrag onderzocht kan worden.

In **hoofdstuk 5** onderzochten we statische tests (pen-en-papier tests) en dynamische tests (een observatieschaal, een ecologisch-valide dubbeltaak en een VR-simulatie) bij 61 patiënten die een beroerte hebben doorgemaakt. Deze patiënten waren gediagnostiseerd met de cognitieve stoornis *neglect*. Neglect is een aandachtsstoornis, waarbij patiënten een deel van de ruimte negeren terwijl ze niet blind zijn. Dit kan ertoe leiden dat patiënten slechts de helft van hun bord leegeten of mensen die aan de aangedane zijde zitten niet opmerken. Meestal negeren patiënten met schade in de rechterhersenhelft de linkerkant van de omgeving en vice versa (Figuur 2). We ontdekten dat patiënten die uitvielen op dynamische tests ook meer problemen hadden in de motoriek. Patiënten moeten in dynamische tests meerdere dingen tegelijkertijd doen (bijvoorbeeld lopen en zoeken) en de aandachtsfunctie heeft een beperkte capaciteit. Bij motorische problemen gaat er een grote hoeveelheid aandacht van een patiënt naar het lopen om te zorgen dat hij niet valt of ergens tegenaan botst. Er is dan onvoldoende aandacht over om tegelijkertijd te zoeken naar objecten.

Neglect komt vlak na een beroerte bij 30 tot 50% van de patiënten voor. De stoornis heeft een negatieve uitwerking op dagelijkse activiteiten en het herstel van de patiënt. Het is in die periode belangrijk dat de stoornis gediagnostiseerd wordt, zodat de patiënt een passende



Figuur 2. Patiënten met neglect negeren een deel van de ruimte. Patiënten met schade in de rechterhersenhelft negeren meestal de linkerkant van de ruimte.

behandeling krijgt. In **hoofdstuk 6** onderzochten we de meerwaarde van een VR-simulatie in de diagnostiek van neglect ten opzichte van een pen-en-papier test en een observatieschaal. We hebben 47 patiënten met neglect, 54 patiënten zonder neglect en 36 gezonde participanten getest. De VR-simulatie betrof een rijsimulatie, waarbij een weg op een projectiescherm was geprojecteerd en patiënten in het midden van de rechterweghelft moesten rijden. Aan de hand van stuurbewegingen werd zijwind nagebootst, waardoor patiënten moesten bijsturen om op de rechterweghelft te blijven. Het lukte patiënten met neglect niet om in het midden te blijven rijden, waardoor zij soms in de berm terecht kwamen. Tevens liet 6–29% van de patiënten geen neglect zien op de pen-en-papier tests en de observatieschaal, maar wel op de rijsimulatie.

VR-simulaties kunnen op verschillende manieren aangeboden worden, zoals op een computerscherm, projectiescherm of met een VR-bril (head-mounted display). Met een VR-bril is de gebruiker volledig opgenomen in de omgeving en kan de gebruiker 360º om zich heen kijken (Figuur 3). Hierdoor maakt een gebruiker op een natuurlijke wijze deel uit van een virtuele omgeving. Het gebruik van VR-simulaties is veelbelovend in de diagnostiek, maar is het gebruik van een VR-bril ook bruikbaar bij patiënten die een beroerte hebben doorgemaakt? In **hoofdstuk 7** vroegen we 88 patiënten die een beroerte hebben doorgemaakt en 66 gezonde participanten twee keer boodschappen te doen in een virtuele supermarkt:

Figuur 3. Het gebruik van een VR-bril om een virtuele omgeving aan te bieden.

één keer met een computerscherm en één keer met een VR-bril. De virtuele supermarkt was ontwikkeld in samenwerking met Atoms2Bits. Zowel de gezonde participanten als de patiënten waren in staat om de taak op beide manieren te voltooien. Ze rapporteerden dat ze zich meer opgenomen voelden in de virtuele omgeving met de VR-bril dan met het computerscherm. Patiënten rapporteerden echter ook meer bijwerkingen met de VR-bril, zoals misselijkheid of duizeligheid. Ondanks de bijwerkingen gaven patiënten aan geen voorkeur te hebben voor het computerscherm of de VR-bril. Dit onderzoek laat zien dat het haalbaar is om VR-simulaties te gebruiken bij patiënten die een beroerte hebben doorgemaakt.

Tot nu toe beschreven we onderzoeken die te maken hadden met de diagnostiek, maar ook op het gebied van behandeling kan technologie een uitkomst bieden. De huidige behandeling richt zich op het aanleren van strategieën om te compenseren voor de cognitieve problemen. Een patiënt wordt bijvoorbeeld geleerd om een boodschappenlijstje te gebruiken om te compenseren voor een geheugenstoornis. Door nieuwe inzichten in het vermogen van de hersenen om zich te herstellen (neuroplasticiteit) zijn er behandelingen ontwikkeld die het herstel van cognitieve functies proberen te bevorderen. Er is echter nog weinig bewijs dat deze behandelingen werken. In **hoofdstuk 8** onderzochten we aan de hand van een literatuuronderzoek drie behandelingen om de geheugenfunctie te verbeteren: VR-training, hersentraining met computertaken en non-invasieve hersenstimulatie (een methode waarmee hersendelen actief of inactief worden gemaakt door elektrische signalen of een magneetveld). Op basis van een literatuuronderzoek, vonden we 3 artikelen over VR-training, 7 artikelen over hersentraining met computertaken en 5 artikelen over non-invasieve hersenstimulatie. VR-training en hersentraining bleken veelbelovend in het verbeteren van de geheugenfunctie. Non-invasieve hersenstimulatie leek geen effect te hebben op de geheugenfunctie. Er is meer onderzoek nodig naar VR-training en hersentraining met computertaken vanwege het beperkte aantal onderzoeken in de literatuur.

Tot slot

In **hoofdstuk 9** worden aanbevelingen gedaan voor toekomstig onderzoek en de klinische praktijk. Dit proefschrift laat slechts het topje van de ijsberg zien van wat er mogelijk is in de cognitieve diagnostiek en behandeling. Cognitieve problemen kunnen op verschillende niveaus gemeten worden. Het ICF-model (International Classification of Functioning) onderscheidt drie niveaus die gerelateerd zijn aan het functioneren: het gaat hierbij om de functie van het lichaam, activiteiten in het dagelijks leven en participatie in de samenleving. Ter illustratie: door een geheugenstoornis (functie van het lichaam) heeft een patiënt moeite

om een gesprek te onthouden (activiteiten in het dagelijks leven) en kan hierdoor niet werken (participatie in de samenleving). De tests die we beschrijven brengen cognitieve problemen op deze drie niveaus in kaart. We zijn er echter nog niet. De tests moeten verder onderzocht worden voordat ze gebruikt kunnen worden in de klinische praktijk. Aanvullende maten moeten ontwikkeld worden in de digitale tests en de VR-simulaties. Bovendien is het van belang om scores van normgroepen te verzamelen om de prestaties van patiënten mee te kunnen vergelijken. Ten slotte, we includeerden in deze onderzoeken enkel patiënten met NAH, mogelijk kunnen deze instrumenten ook bruikbaar zijn bij patiënten met andere diagnoses waar cognitieve problemen spelen.

Het verhaal van Tamara is een voorbeeld uit talloze verhalen waar NAH zorgt voor een breuk in de levenslijn. Cognitieve problemen zijn van grote invloed op de kwaliteit van leven van patiënten en hun naasten. Het in kaart brengen van cognitieve problemen is van groot belang, omdat de diagnostiek aanknopingspunten biedt voor een behandeling. Met deze onderzoeken hebben we geprobeerd de cognitieve problemen beter te begrijpen, in kaart te brengen en te behandelen, maar we zijn er nog niet. Meer onderzoek is nodig om de cognitieve diagnostiek en behandeling te verbeteren.

L'histoire de Tamara

Le 21 décembre 2015, j'ai été soulevée, je me suis cognée la tête contre un poteau et je suis tombée par terre. J'ai entendu les autres crier : « Oh, c'était juste ! » Mais si, j'avais été cognée ! Le lendemain matin, je n'ai pas immédiatement réalisé mon état. Au cours de cette journée, j'ai remarqué que je ne pouvais pas rester éveillée. Je suis allée voir mon médecin qui m'a conseillée de prendre du repos.

Les premières semaines, j'ai eu mal à la tête et j'étais très fatiguée, ce qui m'a forcé à dormir presque toute la journée. J'avais des problèmes de mémoire, des difficultés à me concentrer et je souffrais de trop de lumière ou de trop de bruit. J'ai dû faire des compromis dans ma vie sociale. Faire du sport, écouter un concert ou aller au cinéma n'était plus possible. En avril 2016, j'ai essayé de reprendre mon travail quelques heures par jour. Ce qui a été très difficile. Je ne pouvais pas m'asseoir longtemps devant l'ordinateur, me concentrer sur mon travail et j'avais remarqué que ma mémoire m'abandonnait régulièrement au contact des clients. Néanmoins, on m'a donné plus de responsabilités. Mes symptômes se sont aggravés, mais j'ai eu du mal à accepter de ne plus pouvoir continuer à fonctionner comme avant.

Le 20 juillet 2016, j'ai été renvoyée par mon médecin chez un neurologue et chez un médecin de rééducation. Ils ont mis des mots sur ce que j'avais vécu : mes plaintes correspondaient à une Lésion Cérébrale Acquise (LCA). Ils m'ont conseillé d'arrêter temporairement mon travail afin que je puisse me reposer et prendre du temps pour le traitement. J'ai eu une évaluation neuropsychologique où mes fonctions cognitives ont été testées par des tests papier-crayon. Il m'a fallu beaucoup d'efforts pour terminer les tests, mais seuls quelques subtils manquements sont apparus. Ce qui aurait dû être un soulagement a plutôt été frustrant pour moi car je ne sentais aucune reconnaissance de ce que je vivais. Ce résultat a également eu des conséquences plus tard. Puisque aucun trouble clair n'était sorti de l'examen, le médecin du travail n'a pas voulu me fournir les mesures nécessaires pour que je reprenne tranquillement mon travail, ce qui m'avait été recommandé par le médecin de rééducation.

Nous sommes 5 ans plus tard et mon rétablissement a été difficile. Ces dernières années, plusieurs personnes atteintes de LCA incomprises m'ont contacté. Il y a encore beaucoup d'amélioration en terme de diagnostic, d'accompagnement et de traitement pour ces patients.

Résumé en français

Du papier-crayon à la technologie
Vue d'une autre approche

L'histoire de Tamara est un exemple parmi d'innombrables histoires où des lésions cérébrales chamboulent le cours d'une vie. Tout change d'un jour à l'autre. LCA est le diagnostic le plus courant en médecine de rééducation aux Pays-Bas. Les lésions cérébrales des patients atteints de LCA surviennent après la naissance. Ces lésions peuvent être causées par une cause interne, comme un accident vasculaire cérébral (hémorragie cérébrale ou infarctus cérébral), comme des processus expansifs (tumeur), comme des infections (méningite) ou par une cause externe telle une lésion cérébrale traumatique (recevoir un coup sur la tête due à une chute ou à une collision). Chaque année aux Pays-Bas, 40 000 patients ayant subi un accident vasculaire cérébral et 20 000 patients ayant une lésion cérébrale traumatique sont hospitalisés, soient les deux causes les plus courantes de LCA. En plus des conséquences physiques visibles comme une hémiplégie, une LCA a également des conséquences non physiques, telles que des troubles cognitifs. La cognition est un terme générique désignant diverses fonctions de la pensée, telles que la mémoire, l'attention et le langage.

La neuropsychologie s'intéresse à la relation entre le cerveau et le comportement, l'émotion et la cognition. Les neuropsychologues sont impliqués dans le diagnostic et le traitement des enfants et des adultes atteints de maladies neurologiques ou psychiatriques. Les neuropsychologues sont consultés lorsqu'un patient signale des troubles cognitifs, tels que l'oubli ou un problème de concentration. Les problèmes cognitifs affectent souvent tous les domaines de la vie au domicile, au travail, dans les loisirs ou dans les rencontres sociales. Lorsque les patients sont dans une impasse au niveau de leur vie quotidienne, une rééducation cognitive leur est conseillée. Ce protocole de rééducation commence par un diagnostic pour identifier les fonctions cognitives affectées par la lésion. Celui-ci comprend un examen neuropsychologique consistant en une anamnèse avec le patient et un de ces proches et en un test neuropsychologique. Un plan de traitement est élaboré en fonction des résultats du test.

Partie 1 : Plaintes cognitives : l'expérience d'un patient et de son proche

La première étape du diagnostic est l'entretien avec un patient et un proche (partenaire, parent, ami) : l'anamnèse. Le but principal de l'anamnèse est d'obtenir des informations sur l'histoire de la maladie et son évolution, la gravité et les conséquences des plaintes dans la vie quotidienne. Outre l'histoire du patient, l'histoire d'un proche est également écoutée. Ces histoires ne correspondent pas toujours. Cela peut indiquer qu'ils ont une perception différente des plaintes. Il est donc important d'obtenir des informations des deux parties. Des questionnaires peuvent être utilisés pour soutenir l'échange. Cependant, les questionnaires

actuels n'utilisent pas d'exemples quotidiens. Les patients ont souvent des difficultés à répondre à des questions telles que "Avez-vous des problèmes d'attention ?" Utiliser un exemple dans la vie quotidienne peut les aider : "Êtes-vous capable de vous concentrer sur votre travail sans être distrait par les choses qui se passent autour de vous ?" Cela donne également un aperçu des domaines de la vie dans lesquels il est gêné, comme au travail ou dans la conduite de sa voiture. Dans le **chapitre 2**, nous avons décrit l'élaboration d'un questionnaire visant les plaintes cognitives dans la vie quotidienne. Nous avons développé le questionnaire *Cognitive Complaints – Participation* (CoCo-P) basé sur une revue de la littérature, des interviews avec des patients et des réunions avec des praticiens, des psychologues, des médecins de rééducation et des experts en cognition. Le questionnaire a été présenté à 46 patients atteints de LCA, à 33 proches et à 102 participants en bonne santé. Les patients ont signalé la plupart des plaintes cognitives pendant leur travail ou leur formation, leurs loisirs et leurs contacts avec amis, famille et environnement. Les participants en bonne santé ont signalé très peu de plaintes. Les comptes rendus des proches et des patients sur le niveau de plaintes de ces derniers ne semblaient pas toujours correspondre. Les patients ont signalé plus de plaintes que leurs proches. Cette constatation peut montrer que les patients sous-estiment leur propre fonctionnement (et signalent donc plus de plaintes) ou que les membres de la famille surestiment leur fonctionnement (et signalent donc moins de plaintes). Les patients peuvent avoir une compréhension réduite de leurs propres capacités. Il peut également être difficile pour d'autres, même pour un proche, d'observer des plaintes cognitives. Le CoCo-P s'est avéré être un outil prometteur pour les évaluations systématiquement. Ajouter un questionnaire à l'anamnèse peut éviter que des plaintes ne soient oubliées.

Partie 2 : Tests neuropsychologiques digitaux : mesurer des fonctions cognitives

Lorsque l'anamnèse est terminée, le test neuropsychologique est utilisé pour tester les fonctions cognitives du patient. Le test consiste en différents tests papier-crayon qui évaluent des fonctions cognitives spécifiques. Par exemple, on demande aux patients de se souvenir d'une liste de mots ou de dessiner une figure complexe. Le test est généralement passé dans une pièce calme, avec le moins de distractions externes possibles. Cette situation de test dans le calme garantit des performances optimales. La performance du patient est évaluée en examinant le nombre de réponses correctes ou le temps qu'il lui a fallu pour l'effectuer. La performance est comparée à la performance d'un groupe de référence (un grand groupe de personnes en bonne santé, du même sexe, du même âge et du même niveau d'éducation).

De cette façon, un neuropsychologue peut évaluer si la performance du patient est égale, meilleure ou plus mauvaise que le groupe de référence. Sur la base des résultats et des observations du neuropsychologue, un profil cognitif est formé : fonctions qui ont été affectées et fonctions qui ont été relativement épargnées.

Comme le montre l'histoire de Tamara, les tests papier-crayon ne sont parfois pas assez sensibles pour détecter des problèmes cognitifs légers. Le principal avantage des tests digitaux est que les performances du patient sont enregistrées en totalité. En plus du score final (comme le nombre de réponses correctes ou le temps pris), les neuropsychologues disposent de plus d'informations pour évaluer les performances. Le test digital a été développé en collaboration avec Philips Research, où un patient se voit proposer des tests sur une tablette utilisant un stylet (Figure 1). Comme Tamara le raconte dans son histoire, les patients atteints de LCA peuvent être hypersensibles à la lumière vive, ce qui rend le travail avec un ordinateur, difficile. Dans le **chapitre 3**, nous avons examiné s'il était possible de mener un examen de test digital complet chez 59 patients ayant eu un accident vasculaire cérébral, 61 patients avec une lésion cérébrale traumatique et 159 participants en bonne santé. Les patients et les participants en bonne santé l'ont terminé et l'ont vécu comme positif. Nous avons également découvert que les normes basées sur le groupe de référence pour les tests papier-crayon ne peuvent pas être aveuglement utilisées pour les tests digitaux. Par exemple,

Figure 1. Un examen composé de différents tests digitaux pour évaluer les fonctions cognitives.

l'écran de la tablette étant plus lisse les patients dessinent moins précisément que sur le papier. Enfin, nous avons constaté que les participants qui avaient plus d'expérience avec une tablette électronique ne réussissaient pas mieux aux tests digitaux. Il s'agit d'une découverte importante, car la méthode du test (papier-crayon ou digital) ne doit pas influencer les performances du patient.

Au **chapitre 4**, nous avons développé une mesure pour évaluer la stabilité d'une performance. Par exemple, les patients atteints de LCA peuvent faire un démarrage rapide, mais ne peuvent pas maintenir leur tempo jusqu'à la fin du test, contrairement aux participants en bonne santé. Jusqu'à présent, cela a été observé à l'œil nu par un neuropsychologue. Cependant, les observations sont une mesure subjective, de sorte que les évaluations peuvent différer entre les neuropsychologues. Lors des trois tests digitaux, nous avons développé une mesure permettant d'objectiver la stabilité de la performance sur la base d'un score. De cette façon, les neuropsychologues ont non seulement le score final, mais également un score sur *la façon* dont un patient est arrivé à ce score final. Il s'est avéré que les patients atteints de LCA avaient des performances moins stables que les participants en bonne santé. De plus, 4 à 15% des patients avaient un « bon » score final, mais des performances instables.

Partie 3 : Technologie avancée : l'interaction avec l'environnement !

Les neuropsychologues doivent se prononcer sur le fonctionnement quotidien du patient. Dans de nombreux cas, cela est basé sur le profil cognitif obtenu par les tests neuropsychologiques papier-crayon. Cependant, ces tests statiques soit papier-crayon soit digitaux, effectués en autres dans une pièce calme avec le moins distraction possible, ne correspondent pas à la dynamique de la vie quotidienne. Cependant dans la vie de tous les jours, il lui faut réussir dans un environnement animé, comme dans un *openspace*. Des tests dynamiques tels que des questionnaires d'observation et des doubles tâches écologiquement valides ont été développés pour évaluer les fonctions cognitives dans une situation quotidienne. Les doubles tâches écologiquement valides sont des tâches qui sont administrées dans une situation quotidienne, comme le *Multiple Errands Test* (une tâche de planification dans un centre commercial) ou le *Mobility Assessment Course* (une tâche de recherche dans un couloir). Un des inconvénients de ces types de tâches est qu'elles sont effectuées dans un environnement qui ne peut pas être entièrement contrôlé. Dans un centre commercial il peut être très calme à un moment donné et très fréquenté, le suivant. Dans une situation quotidienne, il n'est pas possible d'ajouter ou de supprimer des stimuli pour voir comment cela affecterait le patient. Les développements technologiques actuels en réalité virtuelle (RV) peuvent fournir une solution. La RV offre la

possibilité de tester des personnes dans un environnement virtuel qui imite la vie quotidienne, comme un supermarché. Il y a donc un contrôle total sur l'environnement virtuel, permettant d'ajouter ou de supprimer des sons, des produits et des acheteurs. Chaque action d'un patient est enregistrée, de sorte que l'influence des stimuli sur le comportement peut être étudiée.

Dans le **chapitre 5**, nous avons étudié des tests statiques (tests papier-crayon) et des tests dynamiques (questionnaires d'observation, double tâche écologiquement valide et simulation RV) chez 61 patients ayant subi un accident vasculaire cérébral. Ces patients avaient reçu un diagnostic de déficit cognitif : héminégligence. L'héminégligence est un trouble déficitaire de l'attention, par lequel les patients ignorent une partie de l'espace sans être aveugles. Cela peut amener les patients à ne manger que la moitié de leur assiette ou à ne pas remarquer les personnes assises du côté affecté. En règle générale, les patients atteints de lésions de l'hémisphère droit ignorent le côté gauche de l'environnement et vice versa (Figure 2). Nous avons constaté que les patients qui échouaient aux tests dynamiques avaient également plus de problèmes de motricité. Dans les tests dynamiques, ils doivent faire plusieurs choses en même temps (par exemple, marcher et chercher) et la fonction d'attention a une capacité limitée. En cas de problèmes de motricité, le patient accorde une grande attention à la marche afin de s'assurer qu'il ne tombe pas ou ne heurte rien. Il n'y a alors pas suffisamment d'attention pour rechercher simultanément des objets.

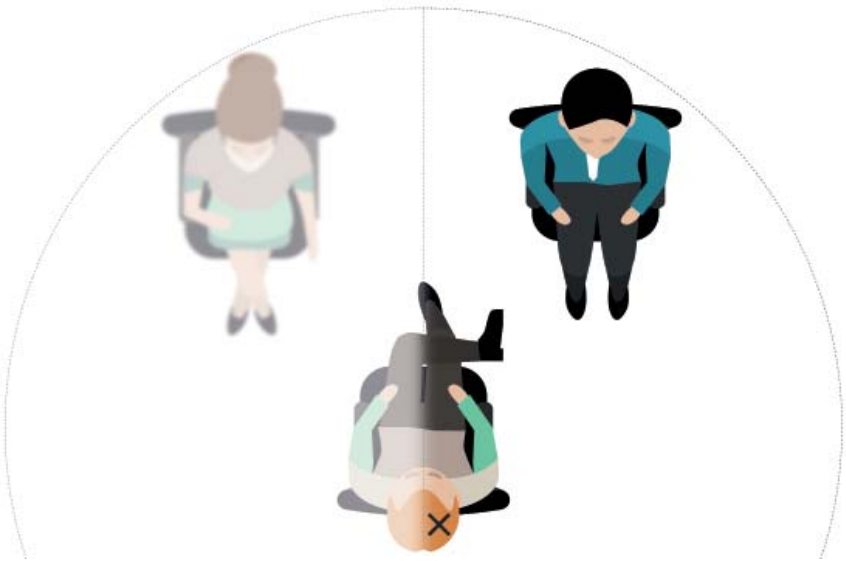


Figure 2. Les patients présentant une héminégligence ignorent une partie de l'espace. Ceux ayant des lésions de l'hémisphère droit ignorent généralement le côté gauche de l'espace.

L'héminégligence survient peu de temps après une LCA pour 30 à 50% des patients. Le trouble affecte négativement les activités quotidiennes et le rétablissement du patient. Il est important pendant cette période que le trouble soit diagnostiqué afin qu'il reçoive un traitement approprié. Dans le **chapitre 6**, nous avons étudié la plus-value d'une simulation RV dans le diagnostic de l'héminégligence par rapport au test papier-crayon et questionnaires d'observation. Nous avons testé 47 patients présentant une héminégligence, 54 patients sans héminégligence et 36 participants en bonne santé. La simulation RV était une simulation de conduite, une route était projetée sur un écran et les patients devaient conduire au milieu de la moitié droite de la route. Un vent latéral était simulé sur le volant, ce qui signifiait que les patients devaient faire des ajustements de conduite pour rester sur le côté droit de la route. Les patients ayant une héminégligence ne réussissaient pas à rester au milieu de la partie droite de la route, ce qui provoquait une descente dans le fossé. En plus, 6 à 29% des patients n'ont pas montré pas d'héminégligence sur le test papier-crayon et la questionnaire d'observation, mais l'ont montré sur la simulation virtuelle de conduite.

Les simulations RV peuvent être présentées de différentes manières, comme sur un écran d'ordinateur, un écran de projection ou avec des lunettes RV (*head-mounted display*). Avec les lunettes RV, l'utilisateur est entièrement absorbé par l'environnement et peut voir à 360 ° (Figure 3). En conséquence, il fait partie naturellement de l'environnement virtuel.

Figure 3. Utilisation de lunettes RV pour créer un environnement virtuel.

L'utilisation de simulations RV est prometteuse dans le diagnostic. Mais on peut se demander si l'utilisation de ces lunettes peut être utile aux patients ayant subi une LCA. Au **chapitre 7**, nous avons demandé à 88 patients présentant une LCA et à 66 participants en bonne santé de faire deux fois les courses dans un supermarché virtuel : une fois avec un écran d'ordinateur et une fois avec des lunettes RV. Le supermarché virtuel a été développé en collaboration avec Atoms2Bits. Tous ont pu accomplir la tâche des deux manières. Ils ont indiqué qu'ils se sentaient plus présents dans l'environnement virtuel avec les lunettes RV que sur l'écran de l'ordinateur. Cependant, les patients ont également signalé plus d'effets secondaires avec les lunettes RV, tels que des nausées ou des étourdissements. Malgré ces effets secondaires, ils ont indiqué qu'ils n'avaient aucune préférence entre les deux. Cette recherche montre qu'il est possible d'utiliser des simulations de réalité virtuelle chez des patients ayant subi une LCA.

Jusqu'à présent, nous avons décrit des études liées au diagnostic, mais la technologie peut également offrir une solution pour le traitement. Le traitement actuel se concentre sur des stratégies d'apprentissage pour compenser les problèmes cognitifs. Par exemple, un patient apprend à utiliser une liste de courses pour compenser un trouble de la mémoire. De nouvelles connaissances sur la capacité du cerveau à se rétablir (la neuroplasticité) ont conduit au développement de traitements qui tentent de favoriser la récupération des fonctions cognitives. Cependant, il y a peu de preuves que ces traitements fonctionnent. Dans le **chapitre 8**, nous avons étudié grâce à une revue de la littérature trois traitements pour améliorer la fonction de la mémoire : l'entraînement en réalité virtuelle, l'entraînement du cerveau à l'aide de tâches informatiques et la stimulation cérébrale non invasive (méthode par laquelle des parties du cerveau sont rendues actives ou inactives par des signaux électriques ou un champ magnétique). Sur la base d'une revue de la littérature nous avons trouvé trois articles sur l'entraînement en réalité virtuelle, 7 articles sur l'entraînement cérébral avec des tâches informatiques et 5 articles sur la stimulation cérébrale non invasive. L'entraînement en réalité virtuelle et l'entraînement cérébral se sont révélés prometteurs pour améliorer la fonction de mémoire. La stimulation cérébrale non invasive ne semble pas affecter la fonction de la mémoire. Des recherches supplémentaires sont nécessaires sur l'entraînement en RV et sur l'entraînement cérébral avec des tâches informatiques en raison du nombre limité d'études dans la littérature.

Finalement

Le **chapitre 9** fournit des recommandations pour la recherche future et la pratique clinique. Cette thèse ne montre que la pointe de l'iceberg, ce qui est possible dans le diagnostic et le traitement cognitifs. Les problèmes cognitifs peuvent être mesurés à différents niveaux. Le

modèle CIF (Classification Internationale du Fonctionnement du handicap et de la santé) distingue trois niveaux liés au fonctionnement : il s'agit de la fonction du corps, des activités de la vie quotidienne et de la participation à la société. Par exemple : en raison d'un trouble de la mémoire (fonction du corps), un patient a du mal à se souvenir d'une conversation (activité de la vie quotidienne) et est donc incapable de travailler (participation à la société). Les tests que nous décrivons identifient les problèmes cognitifs à ces trois niveaux. Cependant, nous n'en sommes pas encore là. Les tests devront être approfondis avant de pouvoir être utilisés dans la pratique clinique. Des mesures supplémentaires devront être développées dans les tests digitaux et les simulations RV. De plus, il est important de rassembler les scores des groupes de référence afin de pouvoir les comparer aux performances des patients. Dans ces études, nous n'avons inclus que des patients atteints de LCA. Ces instruments pourraient également être utiles pour les patients ayant d'autres diagnostics impliquant aussi des problèmes cognitifs.

L'histoire de Tamara est un exemple parmi d'innombrables histoires où une LCA provoque un choc dans l'histoire d'une vie. Les problèmes cognitifs ont un impact majeur sur la qualité de vie des patients et de leurs proches. L'évaluation des problèmes cognitifs est d'une grande importance, car le diagnostic offre des points de départ pour le traitement. Avec ces études, nous avons essayé de mieux comprendre, d'évaluer et de traiter les problèmes cognitifs, mais nous n'y sommes pas encore. Des recherches supplémentaires seront nécessaires pour améliorer le diagnostic et le traitement cognitifs.

Dankwoord

Anything is possible if you have the right people there to support you
– Misty Copeland

Veel mensen hebben direct of indirect bijgedragen aan dit promotietraject. Graag wil ik iedereen bedanken die betrokken is geweest in de afgelopen jaren.

De deelnemers

Allereerst alle deelnemers die hebben meegedaan aan de verschillende onderzoeken. Ik hoop dat jullie weten dat jullie bijdrage van grote waarde is en dat we het niet voor lief nemen. Ik wil jullie bedanken voor jullie welwillendheid mee te doen aan deze onderzoeken.

De deelnemers die hun verhaal hebben verteld in dit proefschrift. Beste allemaal, wat bijzonder dat jullie jullie verhaal met mij hebben willen delen. Op deze manier is mijn proefschrift niet alleen een verzameling van wetenschappelijke artikelen, maar ook een verzameling van verhalen van mensen met niet-aangeboren hersenletsel. Ik kan jullie niet genoeg bedanken. In het bijzonder wil ik Tamara bedanken, mijn lieve vriendin sinds we 12 jaar zijn. Wat moedig dat je je verhaal hebt durven vertellen en dat je op de omslag van dit proefschrift durfde te staan. Ik ben trots op jou, hoe je in het leven staat, wat je achter je hebt gelaten, en wat nog voor je ligt.

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Paranimfen

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About the author

Curriculum vitae
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Curriculum vitae

Lauriane Spreij was born on January 27th 1990 in a little village in France close to Paris, Morainvilliers. She moved to Ermelo, the Netherlands, in 1992, where she completed her primary and secondary education (VWO) and developed a profound love for classical ballet. In 2009 she started the Certificate in Ballet Teaching Studies (CBTS) at the Royal Academy of Dance and a bachelor education in Psychology at Utrecht University. In 2011 she achieved her certificate for ballet teaching and in 2012 her bachelor degree in psychology. After a gap year in South-East Asia, Lauriane pursued her interest in Clinical Neuropsychology and started her master education at Utrecht University. She did a research internship at De Hoogstraat Rehabilitation Centre and a clinical internship at Tergooi Hospital in Blaricum and Hilversum. After obtaining her master degree in 2015, she started as a PhD student at the Center of Excellence for Rehabilitation Medicine, a collaboration between De Hoogstraat Rehabilitation Centre and the University Medical Center Utrecht, under supervision of Prof. dr. Anne Visser-Meily and Dr. Tanja Nijboer. Lauriane worked for four years on several projects concerning the virtual supermarket (in collaboration with Atoms2Bits), the digital neuropsychological assessment platform (in collaboration with Philips Research) and the Cognitive Complaints – Participation Inventory. During her PhD, she coordinated the projects, included over 900 participants, supervised master students, presented her work on (inter)national conferences, and wrote this dissertation. She followed the research educational program "Clininal and Experimental Neuroscience" at the Graduate School of Life Sciences at Utrecht University. She was – and still is – a board member of the Dutch Neuropsychological Society.

In January 2020, Lauriane started a post-master clinical training program (*opleiding tot Gezondheidszorgpsycholoog*) at the department of Neurology and Neurosurgery, at the University Medical Center Utrecht. The second year of the training program will take place at the Altrecht Mental Health Institution.

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