Cognitive Impairment in Patients with Multiple Sclerosis: Evaluation of Established and Novel Neuropsychological Assessment Strategies

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1. Introduction

1.1. Multiple Sclerosis

1.1.1. Relevance and epidemiology

Multiple Sclerosis (MS) is a chronic degenerative disease of the central nervous system (CNS). Up to 2.5 million people are diagnosed with MS worldwide (WHO, 2004). In Germany, approximately 120,000 people are affected and the yearly incidence rate is estimated to be 3.5-5 per 100,000 inhabitants (Compston, 2006; Hein & Hopfenmüller, 2000).

The typical onset of MS is between the ages of 20 and 40, however, children, teenagers and older adults can be affected as well (Bobholz & Gremley, 2011). Overall, women are affected more often than men with a ratio of 2-3 to 1 (DeLuca & Nocentini, 2011). Also, MS is more prevalent in countries of higher latitude, i.e., countries farther away from the equator (Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011).

MS is the most frequent neurological disorder that leads to permanent disabilities in younger adults (DGNLL, 2014) and although modern treatment helps to slow down the disease progression and to ease many of its symptoms, MS itself can neither be cured nor prevented. The economic effects are huge due to the fact that MS-patients have more absences from work, retire early, and need expensive treatment (Flachenecker et al., 2005). The annual costs add up to an estimate of 33,000 Euro per patient and year in Germany (DGNLL, 2014).

1.1.2. Symptoms and disease course

There are at least four distinct, clinical courses that are used to describe MS-related disease activity (DGNLL, 2014):

(1) Clinically isolated syndrome (CIS): First manifestation of symptoms that persist for at least 24 hours and suggest demyelination. Symptoms can include one or more neurological function. About half the patients with CIS convert to a clinical, definite MS within two years (D'Alessandro et al., 2013).

(2) Relapsing-remitting MS (RRMS): The most frequent course at disease onset. This stage is characterized by sudden manifestations of neurological symptoms ("relapses") which are followed by complete or partial recovery over the course of 6-8 weeks ("remission"). In untreated MS, the average relapse rate is 1.8 per year. The relapse rate typically decelerates over the years.

(3) Secondary progressive MS (SPMS): The majority of patients with an initial RRMS (i.e., 80%) convert to SPMS after an average of 10 years. This course is characterized by progressive, neurological worsening independently of relapses, which occur less frequent or not at all.

(4) Primary progressive MS (PPMS): This course is prevalent in about 10 to 15% of MS patients. It is characterized by progressive, neurological decline, from the disease onset, and absence of clear relapses and remissions. To classify patients with occasional relapses additional to the progressive decline, the term progressive relapsing MS has been introduced.

Additionally, the concepts of benign MS and malign MS have been introduced to contrast patients with a very mild (minor disabilities after 15 and more years) as opposed to a very severe disease course (rapid worsening leading to severe disabilities or death soon after disease onset) (Correale, Peirano, & Romano, 2012).

Several different neurological functions can be impaired by MS and therefore the clinical manifestation can vary considerably between individuals. Most prevalent are physical symptoms such as sensory disturbances in limbs (e.g., paresthesia), distorted vision, and motor disturbances (e.g., spasms, ataxia). Other common symptoms include pain, dysarthria, dysphagia, and dysautonomia (especially affecting bladder, intestinal, and sexual functions) (Bobholz & Gremley, 2011). Patients with MS are also frequently affected by "invisible" neuropsychological symptoms (DGNLL, 2014) such as cognitive impairment, disturbed mood and affective regulation (i.e., major depression, bipolar disorder, emotional incontinence, and euphoria), anxiety, paranoia, apathy/fatigue, and alteration of personality (DeLuca & Nocentini, 2011; Hafler et al., 2005; Haussleiter, Brüne, & Juckel, 2009; Siegert & Abernethy, 2005; Tiemann, Penner, Haupts, Schlegel, & Calabrese, 2009).

Disease severity is conventionally measured by using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS is a rating scale that classifies disability as a score between 0 and 10. Scores of 1 and 1.5 refer to minimal signs in one or more functional systems but no disability. Minimal disability in one or two functional systems is classified as 2.0 and 2.5, respectively. An EDSS of 3 and higher indicates at least moderate disabilities and is the cut-off for benign MS. Other milestones are an EDSS of 4 (i.e., not fully ambulatory), 6 (i.e., ambulatory only with aid), and 8 (i.e., essentially restricted to a bed or chair).

The median time to reach an EDSS of 4, 6, and 7 are about 8, 20, and 30 years after disease onset, respectively (Vukusic & Confavreux, 2007). Conversion from RRMS to SPMS typically occurs between the age of 40 and 44 (Olek, 2005). Although several prognostic factors have been identified in epidemiological studies, the results are not consistent and recommendations for an accurate individual prognosis are not yet available (Olek, 2005). Factors that have been associated with a favorable prognosis include female sex, young age at disease onset, winter birth, optic neuritis, and sensory symptoms at onset. In contrast, a progressive course, bladder or bowel symptoms at onset, incomplete recovery from the first attack, a short interval between the first and second attack, early accumulation of disability, motor or cerebellar symptoms at onset may indicate a rather poor prognosis (Langer-Gould et al., 2006). Providing an individual prognosis remains to be a challenge. However, epidemiological data can be used by patients and clinicians to track the individual disease progression relative to reference cohorts (Kister et al., 2013).

1.1.3. Pathophysiology

MS is considered an autoimmune or immune-mediated disease in which the immune system attacks cells in the central nervous system that causes a cascade of inflammation, demyelination and remyelination, oligodendrocyte depletion and astrocytosis, and neuronal and axon degeneration (Compston & Coles, 2008). These processes can affect both parts of the CNS, i.e., the brain and the spinal cord, and result in damaged white and grey matter (Lucchinetti et al., 2011). The characterizing pathology of MS is the accumulation of demyelinated plaques that appear as scars and this gave the disease its name (ancient Greek: sklērós, “hard”). Especially at later stages, whole brain atrophy becomes another

eminent pathology which probably reflects the axonal loss and has the strongest correlation with disease progression.

1.1.4. Treatment

Although there still is no cure for MS, several treatment options are available that have a positive effect on MS-related symptoms and disease progression. In Germany, treatment recommendations are based on three different levels of disease activity, i.e., treatment of acute relapses, treatment of mild to moderate active MS, and treatment of highly active MS (DGNLL, 2014; *Qualitätshandbuch MS / NMOSD*, 2017).

Acute relapses are treated using corticosteroids, usually over the course of three to five days. If the symptoms associated with the present relapse persist, plasma exchange or immuno-adsorption can be applied as second line treatment.

Patients with CIS, RRMS, or SPMS who recovered from an acute relapse are treated with disease modifying drugs. These are immunomodulatory or immunosuppressive substances that decrease the risk of conversion from CIS to MS, reduce the rate of future relapses and slow down disease progression. For patients with PPMS, no disease modifying therapy has been recommended yet, however, a new treatment option was approved by the American Food and Drug Administration in 2017 and may become available to German patients soon (Montalban et al., 2017).

The first approved disease modifying drug for MS was interferon beta which was introduced in Germany in 1995 and replaced the off-label use of azathioprine as the primary choice for MS treatment. In the following years, additional immunomodulatory substances have been approved for treatment of mild/moderately active MS (e.g., glatiramer acetate, 2001; teriflunomide, 2013; dimethyl fumarate, 2014) (*Qualitätshandbuch MS / NMOSD*, 2017). Because most of these substances require frequent self-injections, but do not have an immediate effect, compliance issues are likely. Resolving these is important because clinical trials have shown that the early initiation of treatment cannot be made up by treatment in later stages (Edan et al., 2014) suggesting an early window of therapeutic opportunity (Cocco et al., 2015). A promising approach to improve compliance is based on psychoeducation for newly diagnosed patients (Deppe et al., 2012).

In case of a highly active MS (i.e., either significant disease activity despite immunomodulatory treatment, or severe and rapidly progressing remitting disease course) another set of highly effective DMD is indicated (Gold, 2012). The first line treatment comprises four selective immunosuppressive drugs (i.e., natalizumab, fingolimod, alemtuzumab, and daclizumab) that directly regulate the immune system. On one hand this medication has superior effects on disease activity compared to immunomodulatory drugs. On the other hand, this is accompanied by an increased risk of serious adverse events.

The aforementioned treatment is applied to decrease disease activity in general. In contrast, symptomatic treatment is necessary to treat the particular neurological dysfunctions that each patient experiences individually (DeLuca & Nocentini, 2011). It plays an important role for maintaining quality of life. For example, the spasticity can be managed relatively well by using medical agents and physiotherapy. In case of cognitive impairment, several neurostimulants have been investigated in respect to beneficial effects on cognitive performance and provided mixed results (Grzegorski & Losy, 2017). Neuropsychological rehabilitation could also have a positive effect on cognitive functioning, however, available studies only provide low-level evidence (Rosti-Otajärvi & Hämäläinen, 2014).

1.2. Cognitive impairment in Multiple Sclerosis

1.2.1. Relevance

Cognitive impairment, also referred to as cognitive deficit, cognitive decline or cognitive dysfunction is one of the numerous neuropsychological deficits that patients with MS can experience (Haussleiter et al., 2009). Cognitive impairment has been systematically investigated in MS since the 1980s (Amato, Zipoli, & Portaccio, 2008). Between 43 % and 65 % of MS patients will suffer from cognitive impairment in the course of their disease with deficits typically found in the domains of attention, information-processing speed, executive functioning, memory and learning (Chiaravalloti & DeLuca, 2008). Tests of information-processing speed and visual memory are most frequently affected (Benedict, Cookfair, et al., 2006). Language and intelligence are usually spared and the level of impairment usually stays below that found in dementia (Wegener, Marx, & Zettl, 2013).

Cognitive impairment has significant impact on psychosocial functioning (Amato et al., 1995). For example, employment status, driving safety, coping, symptom management, medication adherence, competence and independence in daily activities, and rehabilitation potential have all been associated with cognitive impairment (Langdon, 2011; Patti, 2009). Consequently, cognitive functioning has been included as an outcome of interest in recent clinical trials (Erlanger et al., 2014; Penner et al., 2012).

Cognitive impairment can be found across all stages of MS, though it seems to be more prevalent in the progressive course, especially in SPMS compared to RRMS and CIS (Potagas et al., 2008). Even patients with benign MS are commonly affected by cognitive impairment which is one reason why the definition of benign MS remains controversial (Amato et al., 2006; Correale et al., 2012).

1.2.2. Definition

For a long time, MS related cognitive impairment has been underestimated by clinicians and was primarily regarded as a symptom of later disease stages (DeLuca & Nocentini, 2011; Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Hoffmann, Tittgemeyer, & von Cramon, 2007). In the past years though, a number of studies investigated cognitive functions in early stage MS and suggested that cognitive impairment can be present already at this stage affecting between 22 % and 54 % of patients (Achiron & Barak, 2003; Amato, Portaccio, Goretti, Zipoli, Hakiki, et al., 2010; Jønsson et al., 2006; Schulz, Kopp, Kunkel, & Faiss, 2006; Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007).

However, it has been criticized that many of these and other related studies were discrepant in respect to methods and material, hindering the understanding of cognitive impairment in MS (Achiron & Barak, 2006; Hoffmann et al., 2007). One of these discrepancies was lacking consent on the definition of cognitive impairment in terms of reliable cut-offs and statistical procedures. The comparability of many cognitive studies is already limited by the fact that different test batteries were used. An inconsistent classification of cognitive impairment would reduce comparability across different studies even more. Additionally, classification based on rather liberal criteria could overestimate the prevalence rates, especially in early disease stages.

Therefore, to promote a more homogenized use of cut-off criteria, the first study of this thesis was conducted to systematically review the use of classification criteria in the literature, to evaluate possible correlations between their usage and sample characteristics (such as disease duration), and to compare classifications resulting from different criteria in a new sample of MS patients.

1.2.3. Assessment batteries

Cognitive assessment in clinical practice is a trade-off between validity, practicality, time, and appropriateness for the patient. Depending on its purpose, the neuropsychological examination may only comprise of a short screening or a comprehensive test battery lasting 2 hours and more and covering a broad range of cognitive functions. For neurological diseases with a circumscribed deficit profile such as MS, validated, disease-specific screenings and test batteries are available that include sensitive tests for impairment in domains typically affected by the disease. These batteries can be used to efficiently detect, quantify and monitor the magnitude of cognitive impairment and may also guide the test selection for a more elaborate assessment in context of descriptive neuropsychological questions (Lezak, Howieson, Bigler, & Tranel, 2012).

In MS, tests of information-processing speed and working memory are recommended to screen for cognitive impairment (Rocca et al., 2015). Tests such as the Mini-mental state examination that are commonly used to screen for cognitive deficits in other patient groups, do not have sufficient sensitivity for the cognitive deficits related to MS (Aupperle, Beatty, Shelton, & Gontkovsky, 2002; Beatty, Goodkin, Hertsgaard, & Monson, 1990; Engel, Greim, & Zettl, 2007). The same holds true for self-report measures (Benedict et al., 2004). In past years, the symbol digit modalities test (SDMT) has become a standard screening test in MS additionally to the paced auditory serial addition test (PASAT) (Parmenter & Weinstock-Guttman, 2007).

A more detailed screening for MS-related cognitive impairment can be accomplished by using the brief repeatable battery of neuropsychological tests (BRB-N) (Rao, Leo, Bernardin, & Unverzagt, 1991) which is one of the most frequently used test batteries for MS patients. With a duration of 20 minutes, it is very time efficient. This battery assesses information-

processing speed (SDMT, PASAT), verbal memory (selective reminding test), visual memory (10/36 spatial recall test), and verbal fluency (word list generation).

The minimal assessment of cognitive function in MS (MACFIMS) is the most comprehensive standardized test battery for MS (Benedict et al., 2002). It lasts approximately 90 minutes and provides additional information on spatial processing and executive functioning. However, the examiner needs to be experienced or well trained in applying these tests.

Therefore, a recent attempt by an international committee of experts was made to establish a very brief, easy accessible and easy to administer test battery to assess MS patients worldwide, even in small centers with staff members that may not have been trained in neuropsychology. The proposed, brief international assessment of cognition for MS (BICAMS) (Langdon et al., 2012) comprises the SDMT and the learning trials of two popular memory test: the California verbal learning test (CVLT) and the brief visuospatial memory test (BVMT). BICAMS has been validated since its publication in different languages and countries (Smerbeck et al., 2017) and in respect to a variety of external factors (e.g., Beier et al., 2017; Goverover, Chiaravalloti, & DeLuca, 2016).

The aforementioned assessment batteries implemented traditional cognitive tests which have been constructed on a very similar theoretical foundation base (Lezak et al., 2012). In essence, cognitive functioning is separated into distinct domains or classes that are assessed by applying specific test paradigms. Key domains are attention (including concentration, information-processing speed, working memory), visuospatial skills, memory, language, executive functioning, and intelligence (concept formation, reasoning) (Bobholz & Gremley, 2011; Strauss, Sherman, & Spreen, 2006). These are further divided into subdomains, e.g., verbal memory versus visual memory, or selective versus divided attention. On one hand these theoretical distinctions have “proven useful in psychological assessment generally and in neuropsychological assessment particularly” (Lezak et al., 2012, p. 25). On the other hand, this traditional framework is increasingly challenged by the growing body of knowledge in cognitive neuroscience. Thus, according to Lezak and colleagues, clinical neuropsychologists are well aware of the more sophisticated conceptualizations of cognitive functions in the experimental literature and anticipate the transfer into practice, i.e., the development of novel, neuro-scientific informed tests of specific cognitive functions.

The parametric assessment of visual processing capacity based on the theory of visual attention (TVA) can be considered a novel test (see chapter 1.3). Therefore, the aim of this thesis's third study was to apply TVA-based testing to MS patients at different disease stages and compare the resulting pattern with performance in traditional cognitive tests.

1.2.4. Memory functioning

Memory functioning can be impaired in up to 65% of patients with MS (Rao, Grafman, DiGiulio, Mittenberg, & Et Al, 1993) and might already be present in the first years of the disease (Sicotte et al., 2008). Most commonly affected are episodic and explicit memory, whereas semantic, implicit, and autobiographical memory remains mostly preserved (Prakash, Snook, Lewis, Motl, & Kramer, 2008). Memory deficits are evident in tests of verbal as well as visual memory and the primary core deficit has been attributed to an impaired acquisition (Deluca, Leavitt, Chiaravalloti, & Wylie, 2013; Lafosse, Mitchell, Corboy, & Filley, 2013), although retrieval and storage processes can be disrupted by MS as well (Thornton & Raz, 1997). In respect to verbal memory, three distinct patterns have been identified, i.e., having either normal functioning, mild to moderate impairment, or severe amnesia-like deficits (Beatty et al., 1996).

The exact neurophysiologic processes causing memory impairment in MS are still unclear. However, results from neuroimaging studies are helping to understand the underlying mechanisms. These studies have shown that measures of global cerebral damage (such as brain atrophy) and the amount of white matter lesions, as well as measures of localized damage in strategic areas (such as the hippocampus) are correlated with memory impairment (Rocca et al., 2015). Findings from functional MRI studies suggest an additional modulating role of functional reorganization in early disease stages which might allow an adaptive compensation of structural damage in the memory network by increased functional activation (Hulst et al., 2015). Lately, differential contributions of multiple imaging measures to cognitive impairment have been evaluated by using multivariate designs. These studies confirmed that different global and focal parameters are correlated with different cognitive deficits in parallel and that deep grey matter nuclei have the highest predictive value for global deficits (Daams et al., 2015; Damjanovic et al., 2017; Debernard et al., 2015; Pinter et

al., 2015). However, despite these recent findings, there are still inconsistencies in respect to the presence of memory impairment in early disease stages (e.g., Pardini et al., 2014; Sicotte et al., 2008) and the role of hippocampal atrophy (e.g., Anderson et al., 2010; Sicotte et al., 2008). One reason for these might be related to different neuropsychological assessment strategies. For example several different memory tests have been used in previous studies and information-processing speed as a potential mediator of memory impairment has not been considered (Lafosse et al., 2013; Tam & Schmitter-Edgecombe, 2013).

Thus, the second study of this thesis utilized a multivariate design to evaluate the contribution of structural MRI parameters to memory impairment in MS and in addition, accounted for methodological details regarding memory assessment.

1.3. TVA-based assessment of visual processing capacity

Claus Bundesen's theory of visual attention (TVA) (Bundesen, 1990) is an influential perspective on selective attention. In contrast to other theories, attention is not understood as a mental spotlight that serially processes visual information, but as a parallel processing race between all information in the visual field (Habekost, Petersen, & Vangkilde, 2014). Additionally, TVA is a combined theory of selection and recognition, i.e., the selection of a visual object and its transfer into the visual short-term memory (VSMT) are modeled as a unified mechanism (Kyllingsbaek, 2006). The details of the postulated processing race are specified by a set of mathematical equations (Habekost & Rostrup, 2007) which can be used to develop TVA-based assessment tests of visual processing capacity (Foerster, Poth, Behler, Botsch, & Schneider, 2016; Kyllingsbaek, 2006).

1.3.1. Theory of Visual Attention

According to TVA, the brain processes visual information in a two-stage process which can be mathematically formulated (Bundesen, 1990; Bundesen, Habekost, & Kyllingsbaek, 2005; Kyllingsbaek, 2006). In a first stage, all visual objects in the visual field are filtered. For this purpose different basic features of each object (e.g., a certain color or shape) are matched with representations in the visual long-term memory and according to this match are then given a sensory evidence value. This is happening for all objects in parallel and initially

unselective (in the later descriptions of TVA also referred to as the “first wave”). Thereafter, an attentional weight is determined for each object based on the product of sensorial evidence and pertinence (i.e., how relevant a feature is for an individual’s perception at this moment) for every particular feature. Only after this filtering, in a second, selective stage - called pigeonholing – the processing capacity of the visual system is distributed across visual objects depending on (1) their attentional weights, (2) the perception bias for object categories (e.g., identifying letters), and (3) sensory evidence for the object belonging to each of these categories. Thus, the processing speed, i.e., the speed at which a visual object is encoded into the visual short-term memory (VSTM) is determined by sensory evidence, pertinence, and perception bias. Objects with high processing speed have a higher chance to be encoded into VSTM. One object after the other is transferred into VSTM until it is full (capacity is typically around 4) and processing is terminated.

Put differently, visual processing can be considered a race between visual objects for reaching VSTM in time. This race is constrained by the total amount of processing speed and the maximum capacity of VSTM in a person and affected by top-down (e.g., expectations in respect to the visual input; individual long-term memory representations) and bottom-up (sensory evidence of each object, number of relevant categories) factors. For this reason, TVA is considered to be strongly related to the biased-competition model of visual attention (Bublak et al., 2011; Desimone & Duncan, 1995).

In 2005, a neural interpretation of TVA was introduced to demonstrate that the proposed model of visual processing is in accordance with several neurophysiological findings in the central nervous system (Bundesen et al., 2005). Essentially, the authors suggest that from a single cell perspective, filtering alters the number of cortical neurons in which an object is represented, whereas pigeonholing alters the firing rate of cortical neurons for a particular feature. From a structural perspective, the authors propose that visual processing is distributed across the lateral geniculate nucleus, striate and extrastriate cortical areas, pulvinar nucleus of the thalamus, and the thalamic reticular nucleus as a feed-forward loop (Bundesen, Habekost, & Kyllingsbæk, 2011).

1.3.2. Assessment paradigm

The equations provided by TVA can be used to assess the visual processing capacity of a person from performance in two simple tasks. In these, subjects are briefly presented letter arrays and asked to either report all letters ("whole report") or only letters of a certain type which are typically letters of a predefined color ("partial report") (Shibuya & Bundesen, 1988; Sperling, 1960). TVA-based testing usually applies one of these tasks with variable exposure durations of the letter array as the independent variable (typically between 10 and 200 milliseconds) and the number of correctly reported letters as the dependent variable. The number of presented letters is usually kept constant but their placement on the screen is altered randomly.

The number of correctly reported letters is regarded as an outcome measure of how many visual objects were transferred into VSTM as "winners of the race". In accordance with TVA, this number rises with prolongation of exposure duration and the extent to which it does, reflects the total processing rate of a persons' visual system. Additionally, the increase of recognized letters ceases at some point which, according to TVA, is determined by the capacity limit of a subjects' VSTM.

The relation between exposure duration t and reported letters can be modeled for each person as an exponential growth function f(t) (**Figure 1**). From this function the main TVA-based parameters of visual processing can be derived (Habekost, 2015; Kyllingsbaek, 2006): (1) The perceptual threshold t_0 is determined by the curves' origin (f (t) = 0) and represents the minimum exposure duration required for the visual system to transfer any meaningful object into VSTM. (2) The processing rate C is determined by the curves' slope at its origin and represents the number of visual objects that can be processed per second. (3) The VSTM capacity K is determined by the curves asymptote. These parameters can be estimated from data acquired in the whole report. From performance difference between unmasked and masked trials (see below) iconic memory buffering (μ) can be estimated reflecting the additional time a visual percept is available for processing due to visual persistence.

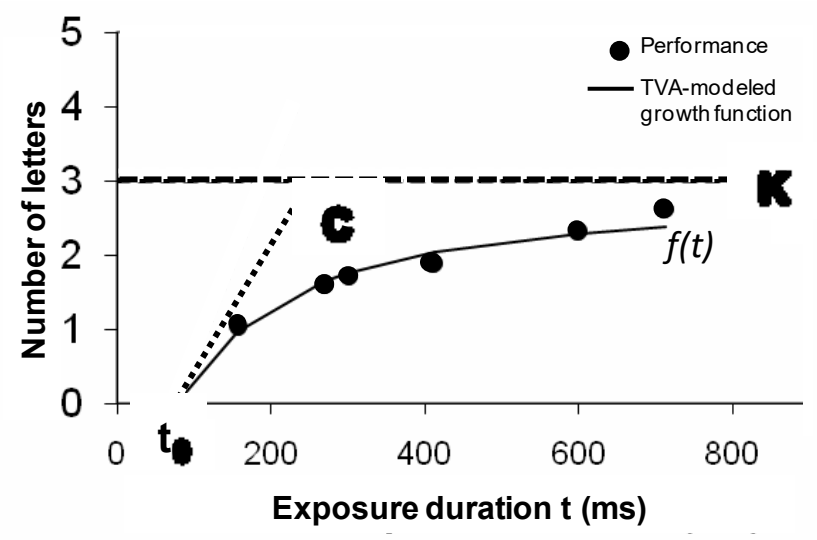

Figure 1. Illustration of TVA-based modelling of visual processing capacity.

A subjects' performance in the whole report task is used to model an exponential growth function f(t) that relates the mean number of correctly reported letters to length of exposure duration. The resulting curve is characterized by three parameters reflecting visual processing capacity: The slope at the curve's origin determines the processing rate C, the asymptote determines visual short-term-memory storage capacity (K); the origin determines the perceptual threshold (t0).

Two standard paradigms for TVA-based assessment of visual processing capacity are in use (**Figure 2**). The first one was introduced by Duncan et al. (1999), the second one by Vangkilde et al. (2011). In the version of Duncan et al., five letters are displayed in a vertical column either to the left or right of a fixation cross. Exposure times are individually adapted and half the trials are masked. In the partial report one or two letters of different color (targets or distracters) are shown at four possible locations around fixation. The version of Vangkilde et al., also called CombiTVA, is a combination of whole and partial report trials. Up to six letters are displayed in a circle around the fixation cross and are always post-masked. Furthermore, the set of exposure durations is fixed, i.e., the letters are presented to each subject at the same exposure durations ranging between 10ms and 200ms. The most recent development was a modified version of the CombiTVA whole report for a virtual reality device that could simplify a feasible and reliable TVA-based assessment (Foerster et al., 2016).

The mathematical estimation of the TVA-based parameters from a set of behavioral data can be performed by using a program package provided by Kyllingsbaek (2006). It allows specifying different models to whole or partial report paradigms as well as subsequent parameter estimation.

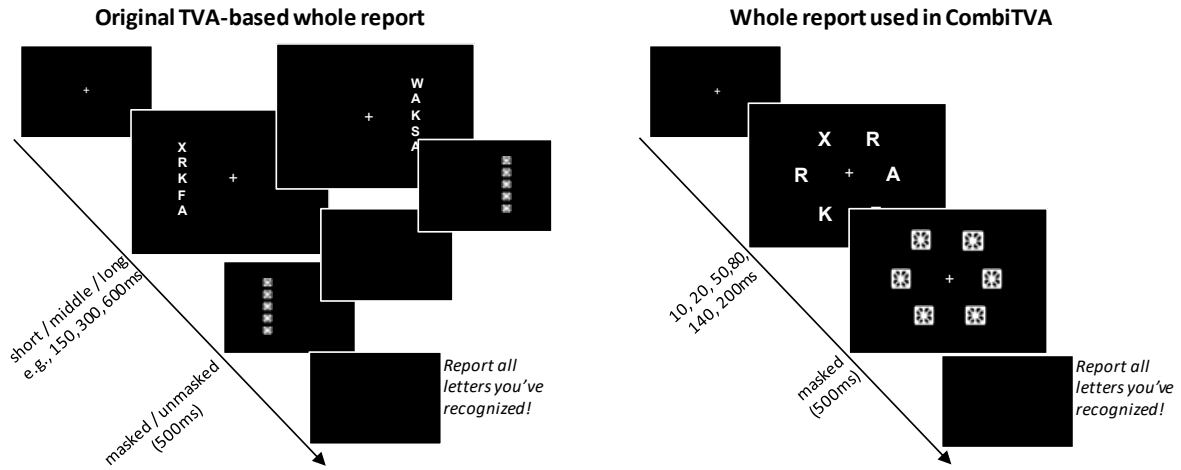

Figure 2. Two standard paradigms for TVA-based assessment of visual processing capacity.

The whole report version devised by Duncan et al. (1999) and the one devised by Vangkilde et al. (2011) are illustrated. Both versions differ in respect to stimuli display (quantity, size, and layout of the letters), exposure duration (fixed vs. individually adapted) and masking (unmasked trials included or not).

1.3.3. TVA-based assessment in clinical samples

TVA-based assessment has several qualities that makes it valuable for the evaluation of clinical samples (Habekost, 2015). Firstly, it has a profound theoretical grounding and cognitive specificity. Secondly, it assesses visual processing independently of reaction time and motor response. Thirdly, the whole and partial report tasks are easy to understand and executed. Hence, it comes to no surprise, that TVA-based assessment has been used in over 30 clinical studies. Up to now, patients suffering from neglect, thalamic stroke, parietal stroke, frontal stroke, simultanagnosia, alexia, dyslexia, Huntington's disease, mild cognitive impairment, Alzheimer's disease, attention deficit hyperactivity disorder, spina bifida, and preterm birth have been systematically evaluated by using TVA-based assessment (Habekost, 2015). Additionally, results from a first investigation of TVA-based visual processing capacity in a small heterogeneous sample of RRMS patients have been recently reported (Kluckow, Rehbein, Schwab, Witte, & Bublak, 2016).

Upon reviewing these former studies, Habekost (2015) concluded that TVA-based assessment can be used to acquire reliable and specific visual processing deficit profiles. Its cognitive specificity can help to better understand and elaborate attentional deficits

resulting from focal or more generalized brain damage. Additionally, TVA-based testing can pick up on very subtle visual processing deficits in otherwise cognitively, well-functioning individuals (Finke et al., 2015). Kluckow et al. (2016) demonstrated that significant alterations of TVA-based parameters are evident in MS patients who are still relatively high-functioning.

Therefore, assessing the TVA-based profile of visual processing capacity in larger, more homogenous groups of MS patients could help to disentangle its most common cognitive deficit, i.e. slowed information-processing speed and moreover, evaluate how sensitive it is for visual processing deficits in patients with a very early MS or with still well-preserved cognitive functioning.

1.3.4. Correlation with cognitive functioning

A systematic comparison between TVA-based parameters of visual processing and cognitive functioning as assessed by a broad neuropsychological assessment battery in one clinical sample has not been reported yet. However, cognitive functioning in selected cognitive domains has been compared to visual processing capacity in two clinical studies. Bublak et al. (2011) applied the Mini-Mental State Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery in a study of elderly patients with mild cognitive impairment or probable Alzheimer's disease. Their data showed that the total scores of the MMSE and CERAD were moderately correlated with the TVA-based processing rate C and weakly with the VSTM storage capacity K. In contrast, they found no correlations with the perceptual threshold t_0. Kluckow et al. (2016) found a significant correlation between processing rate C and an objective measure of fatigue derived from performance in the paced auditory serial addition test which is a non-visual test sensitive to information-processing speed and working memory deficits ins MS.

More detailed comparisons between TVA-based assessment and standard cognitive test performance were reported by studies of healthy subjects. In their validity study of TVA-based assessment, Finke et al. (2005) applied standard tests of psychomotor speed (alertness, i.e., responsiveness to a simple visual stimulus), spatial distribution of attention (visual scanning, i.e., time to detect a target stimulus in the visual field), top-down control

(stroop test), working memory capacity (visual memory span subtest from the revised Wechsler memory scale), and crystallized intelligence (vocabulary test). They found weak to moderate correlations between TVA-based parameters and congruent traditional tests, e.g., the TVA-based processing rate C was found to be correlated with psychomotor speed (r = -.33), VSTM storage capacity K with working memory (r = .29), and the efficiency of top-down-control α with top-down control (r = .38). In another large-scale study of 325 healthy adults, several conventional tests were applied to derive an index of higher order cognitive functioning (i.e., California Verbal Learning Test II, a stroop adaption, an experimental letter discrimination test) and processing speed (i.e., Digit-symbol substitution test) (Espeseth, Vangkilde, Petersen, Dyrholm, & Westlye, 2014). A pattern of weak correlations between both indices and t_0, C, K, and α were found. However, in a subgroup of elderly an amplified correlation with t_0 was reported, whereas in people below the age of 50, C and K were the predominant correlates. The authors of the study speculated that elevations of the perceptual threshold could indirectly explain age-related cognitive decline that is related to slowing processing speed.

These studies show that TVA-based assessment is valid in respect to assessing intact and impaired cognitive functioning but not redundant. Moreover, they suggest that the correlation pattern changes with the beginning of cognitive decline and this change could be differential depending on the factors causing it. Thus, analyzing correlations between TVA-based visual processing capacity parameters and performance in conventional neuropsychological tests could help to understand whether cognitive impairment in MS is comparable to cognitive decline associated with Alzheimer's disease or rather with decline associated with age-related factors.

1.4. Aim and objectives

The aim of this thesis was to evaluate established and novel neuropsychological assessment strategies for cognitive impairment in MS.

It was shown in chapter 1.2 that established assessment strategies for cognitive impairment in MS have varied in respect to the utilized tests and applied criteria for impairment classification which makes it hard to compare the outcomes between different studies. Therefore the objective of the first study was to review classification criteria for cognitive impairment and compare their outcomes in patients with early and late MS (Fischer et al., 2014).

In chapter 1.2.4 it was shown that several conflicting findings exist in respect to the presence of memory impairment at different stages of MS and its correlation with hippocampal atrophy which might be related to different memory assessment strategies. Thus, the objective of the second study was to investigate memory impairment and structural magnetic resonance imaging correlates in homogenous groups of early and late MS, controlling for a potential information-processing speed deficit, and utilizing multiple memory test paradigms (Köhler et al., 2017).

In chapter 1.2.3 it was argued that established neuropsychological assessment strategies utilize tests that, although proven useful, are increasingly challenged in respect to their theoretical foundation by insights from modern cognitive neuroscience. Thus, in chapter 1.3 an alternative, novel assessment strategy based on a theory of visual attention was introduced that has been successfully applied to patients with a range of neurological and psychiatric conditions. Therefore, the objective of the third study was to assess TVA-based visual processing capacity at different stages of MS and its relationship with cognitive functioning determined by conventional neuropsychological tests.

2. Study one: How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis?

2.1. Introduction

Cognitive impairment (CI), also referred to as cognitive dysfunction, cognitive deficit, and cognitive disorder, is a common symptom of multiple sclerosis (MS) (Langdon, 2011). It has relevance for many aspects of quality of life, such as maintaining employment, daily-living activities, social life, ability to drive, and benefits from in-patient rehabilitation (Patti, 2009). Complex attention, information processing speed, verbal and visual-spatial memory, and executive functions are frequently impaired in MS, whereas intelligence, language, semantic memory and attention span are widely preserved.

The first signs of CI can already be found at the time of MS onset (Achiron & Barak, 2003; Glanz et al., 2007; Potagas et al., 2008; Schulz et al., 2006; Zivadinov, De Masi, et al., 2001). In later disease stages, CI seems to progress in terms of prevalence and severity (Glanz, Healy, Hviid, Chitnis, & Weiner, 2012). The reported prevalence of CI in MS ranges highly, between 40% and 80%. What is the reason for such a large variance?

Two factors that potentially influence prevalence rates are sample composition and neuropsychological assessment (Benedict, 2009). Advanced age, progressive disease course, later disease stage, higher physical disability, fatigue, and depression are sample characteristics that tend to be associated with CI (Patti, 2009). Psychometrically, the classification of CI is based on the comparison of an individual test result to the mean of a normative sample. Commonly, performance below one, one-and-a-half, or two standard deviations (SD) of the normative mean is used as cut-off for impairment classification. By definition, lower cut-offs (e.g., 1 SD) result in higher prevalence rates of CI than conservative cut-offs (e.g., 2 SD).

In neuropsychological practice however, it is common to use a battery of tests instead of a single test. This also affects the prevalence rates of CI, because the likelihood of irrelevant

impaired results rises with an increasing number of obtained scores (Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008). Thus, the outcome of CI is highly influenced by the utilized cut-off and the number of tests (Binder, Iverson, & Brooks, 2009).

In MS, research on cognitive functions focused on finding sensitive and brief test batteries for CI in MS (Langdon et al., 2012), but hardly addressed the issue of classification criteria (Hoffmann et al., 2007). Many studies used standard test batteries like the brief repeatable battery of neuropsychological tests (BRB-N) and defined CI as performance below the fifth percentile on about 20% of test parameters or tests (Benedict, 2009). However, more liberal (Achiron & Barak, 2003; Deloire et al., 2006; Feuillet et al., 2007) or conservative criteria (Hulst et al., 2013), as well as non-standardised test batteries have also been used. Furthermore, some authors defined CI by employing composite indices or domain specific criteria (Camp, Stevenson, & Thompson, 1999; Khalil et al., 2011; Smestad, Sandvik, Landrø, & Celius, 2010).

To our knowledge, there is no study that compared these different classification strategies. Thus, it remains unclear when to utilize which strategy and if different strategies lead to comparable outcomes. For the first time, a review of common classification strategies for CI in MS is provided and their outcomes are compared. Moreover, we evaluate their diagnostic validity in the cognitive assessment of groups in early and late disease stages as compared to matched controls. The major goal is to promote a more homogenized use of classification strategies that allows better comparability of future studies on cognitive impairment in MS.

2.2. Methods

2.2.1. Review

Literature search

Reference lists of recent reviews (Achiron & Barak, 2006; Amato et al., 2008; Chiaravalloti & DeLuca, 2008; Ferreira, 2010; Hoffmann et al., 2007; Langdon, 2011; Prakash et al., 2008) and the online database MEDLINE were searched for original articles on cognitive impairment in MS. Search terms were combinations of “multiple sclerosis”, “cognitive impairment”, “classification” “composite” and “index”.

Selection criteria

Articles were included if they met the following criteria: (1) published between 1999 and 2013 in the English language, (2) classification of cognitive impairment, (3) classification based on test batteries that comprised a minimum of 5 neuropsychological test parameters testing at least 2 cognitive domains. Articles were excluded if the classification criterion was not specified or unclear (e.g., number of relevant test parameters not provided).

Data extraction

The following data were extracted: name of test battery, number of cognitive parameters the classification is based on, critical number of abnormal parameters, SD cut-off, sample characteristics (n, disease course, age, disease duration, percentage of impaired patients).

When possible the criteria were classified with respect to their stringency (liberal, fair, or conservative). This was based on false positive rates, i.e., on how many parameters healthy people fail on a cut-off of 1, 1.5, and 2 SD (Schretlen et al., 2008). For example, assuming that 32% of the parameters in a test battery fall 1 SD below the normative mean in 84 % of healthy controls, we considered criteria that define CI as performance below 1 SD on 32 % ± 6.4 % of test parameters as fair, on less than 25.6 % as liberal, and on more than 38.4% as conservative. The respective figures were 17 ± 3.4 % for the 1.5 SD / 5^{th} percentile cut-off, and 7.5 ± 1.5% for the 2 SD cut-off. Additionally, a continuous measure of stringency (y) was computed by dividing the utilized rate of abnormal parameters (x = critical number of abnormal parameters / total number of relevant parameters) from the aforementioned false positive rates (i.e., y_{1SD}= x / 32; $y_{1.5SD}$= x / 17; y_{2SD}= x / 7.5). Higher y represent more stringent criteria.

Statistical analysis

One-way ANOVAs with Tukey post-hoc tests were performed to determine differences in CI and disease duration. Correlations between the continuous measure of stringency, disease duration and CI were analysed using the nonparametric Spearman's rank correlation coefficient.

2.2.2. New data

Subjects

Seventy-seven patients with a first clinical demyelinating event related to MS or a definite MS diagnosis according to the criteria of McDonald (Polman et al., 2005) were recruited from five multiple sclerosis centres (**Table 1**). The sample was divided into two groups aged between 18 and 55 years, one group having a disease duration less than 2 years from the first clinical event (early MS) and the other group with a disease duration longer than 12 years (late MS). A significant difference in the prevalence of CI can be expected between these groups (Amato, Ponziani, Siracusa, & Sorbi, 2001). The two groups were matched with respect to age at disease onset (+/- three years), gender and educational level (years of education). That means one patient with early MS was matched with two late MS patients. The late MS group was twice as large as the early MS group because their data was going to be used in another study focusing on MRI correlates of late cognitive impairment. Exclusion criteria were a relapse or corticosteroid treatment 4 weeks prior to neuropsychological assessment, visual impairment (>0.2), severe fatigue and depression, alcohol abuse, pregnancy, and other relevant serious neurological and internal medical diseases as well as exclusion criteria for MRI. Depression and fatigue were evaluated with the German version of the Center for Epidemiological Studies Depression Scale (Hautzinger & Bailer, 1993) and the "Wuerzburger Fatigue Inventory for MS" (Flachenecker et al., 2006). Scores of 39 or more and 52 or more were considered indicative of severe depression and fatigue respectively.

Additionally, a group of demographically matched healthy control subjects were recruited. Controls also needed to be free of any neurological and psychiatric conditions, as well as other medical conditions associated with cognitive impairment. All subjects provided their informed consent to participate in the study. The study was approved by the local Ethical Committees. Patients, as well as controls, received financial compensation for their travel expenses.

Table 1. Clinical and demographic variables

	group				p[1]		
	early MS (a)	late MS (b)	controls for early MS (c)	controls for late MS (d)	a-b	a-c	b-d
N	25	52	25	50	N/A	N/A	N/A
Gender (m/f)	8/17	16/36	8/17	14/36	1.000	1.000	0.830
Age (mean±SD years)	29.2±6.7	45.3±7.8	28.6±7.3	44.4±7.7	**0.001**	0.734	0.591
Age at disease onset (mean±SD years)	28.2 (7.0)	28.7 (7.1)			0.78	N/A	N/A
Disease duration (mean±SD years)	1.0±0.8	16.5±5.2			**0.001**	N/A	N/A
Number of relapses past year (mean±SD)	1.5±1.9	0.3±0.7			**0.000**	N/A	N/A
Multifocal involvement at onset[2]	24.0%	23.0%			1.000	N/A	N/A
EDSS[3] (mean±SD)	2.0±1.4	3.6±2.0			**0.001**	N/A	N/A
Using MS medication	96.0%	88.5%			0.257	N/A	N/A
Education ≥12y	36.0%	28.8%	36.0%	26.0%	0.603	1.000	0.830
Depression (CES-D) (mean±SD)	12.8±9.7	13.0±9.2	7.4±4.7	8.8±8.2	0.91	**0.017**	**0.017**
Fatigue (Weimus) (mean±SD)	19.6±16.3	26.6±14.5	6.9±8.3	7.8±10.4	0.06	**0.001**	**0.000**

1: p-values of independent samples t-test, U-test (relapses past year), Fisher's exact test (gender, using MS medication, multifocal involvement)
2: more than one sign or symptom related to MS, e.g., optic neuritis accompanied by muscle weakness
3: EDSS: Expanded Disability Status Scale

Neuropsychological Assessment

Trained psychologists administered an extensive neuropsychological test battery including common tests for attention, memory, and executive function in a single 2-hour session. Responsiveness (alertness), divided attention, and mental flexibility were assessed by using the Computerized Test Battery of Attention (TAP) (Zimmermann & Fimm, 2011). Verbal memory was assessed by the German version of the Rey Auditory Verbal Learning Test (AVLT) (Helmstaedter, Lendt, & Lux, 2001) and by the short form of the Verbal Learning Test (VLT) (Sturm & Willmes, 1999). Visuospatial ability and incidental memory were assessed by the Rey-Osterrieth Complex Figure Test (ROCF) using the Taylor Scoring System (Strauss et al., 2006), while visual learning and memory were measured by the short version of the "Diagnosticum fuer Cerebralschaedigung" (Wolfram, Neumann, & Wieczorek, 1989).

Furthermore, the short form of the Nonverbal Learning Test (NVLT) (Sturm & Willmes, 1999) was used to assess continuous visual recognition learning. Tests were performed in the following fixed order: AVLT (learning), ROCF (copy), alertness, divided attention, flexibility, AVLT (recall, recognition), ROCF (recall), DCS, VLT, and NVLT.

Individual raw scores were converted to standard T-scores based on age- and gender-matched normative data from the corresponding test manuals. Normative data of the attention tests and the VLT and NVLT were also matched in respect to education. Each Rey-Figure was scored independently by two psychologists which a third psychologist used to conduct the final scoring. Fifteen parameters were considered relevant for impairment classification: Alertness: Median reaction time with (1) and without auditory cue (2); Divided Attention: Median reaction time auditory (3) and visual (4), errors (5), omissions (6); Flexibility: Index of overall performance (7); AVLT: Recall trial 1-5 (8), difference trial 5 and delayed free recall (9), recognition (10); ROCF: Delayed recall (11); DCS: Memory index first trial (12), learning index (13); VLT: Difference of true and false positives (14); NVLT: Difference of true and false positives (15).

Cognitive impairment classification

The classification criteria that were identified in the review part of this paper were adapted so that they could be applied on the present 15 parameters. For example, if the reviewed criteria required 3 out of 12 parameters to be abnormal, the equivalent would be 4 out of 15 in our data. To adapt criteria that accounted for cognitive domains (e.g., abnormal parameters in at least two domains), the following domains were defined in our test battery: attention (TAP-Alertness, TAP-Divided Attention), memory (DCS, AVLT, VLT, NVLT), immediate recall (AVLT-trial 1-5, DCS, VLT, NVLT), delayed recall (ROCF, AVLT-trial7, AVLT-recognition), and executive function (TAP-Flexibility).

Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Relevant outcomes were rates of cognitive impairment and inter-rater reliability defined as percentage of patients classified as impaired/unimpaired by two or more classification strategies. Group comparisons of impairment rates were assessed using

Fisher's exact test. Inter-rater reliability was assessed using Kendall's W. Group comparisons of inter-rater reliabilities were tested using repeated measures ANOVA with Bonferroni corrected pair wise comparisons. The alpha error level was set at 0.05.

2.3. Results

2.3.1. Review

Out of 921 screened records, 68 articles were included into the review (**Figure 3**). 70 classification criteria could be identified and grouped into 20 distinct approaches (**Table 2**; **Table e1**). Cognitive performance was mostly evaluated by variations of standard test batteries (BRB-N: 31, MACFIMS: 7, other: 5, nonstandard test battery: 27). Three basic classification strategies are in use:

Strategy 1: Critical number of abnormal parameters

59 criteria utilized a classification strategy based on the number of abnormal parameters, i.e., a person is considered cognitively impaired if he scores abnormally low on a predefined number of scores. Cut-offs for abnormality varied between one and two standard deviations. The 1.5 / 1.68 SD (n = 30) and 2 SD (n = 25) cut-offs were equally common, whereas 1 SD (n = 4), and combinations of 1.5 and 2 SD (n = 2) were used less often. On average, the included studies defined a rate of 22 ± 9.4 % (range: 6 – 5 0%) of abnormal test parameters to be critical for impairment. In six studies, the authors varied the classification strategy by grouping the parameters into tests or domains (e.g. attention, information processing, memory, executive function). Thus, they ensured that only patients who performed abnormally in multiple tests or domains are considered cognitively impaired. Of the 51 criteria that could be evaluated in respect of stringency (i.e., not domain-specific, no combined cut-off), 5 were classified liberal, 17 fair, and 29 conservative.

Strategy 2: Composite score

In eight articles, the formation of composite indices were described which can be used for impairment classification. In three cases, the mean of all normalized scores was used. In one paper, the composite was computed as the sum of only those normalized parameters that

highly intercorrelated and had a mean below T = 50. In three other papers, domain-specific means of normalized scores were used. One other approach was used in which a "global cognitive impairment index" was computed by grading each test score in respect to mean and standard deviations of normative data (Camp et al., 1999).

Strategy 3: Combined criteria

In three papers, classification of CI was based on a combination of composite scores and number of abnormal parameters.

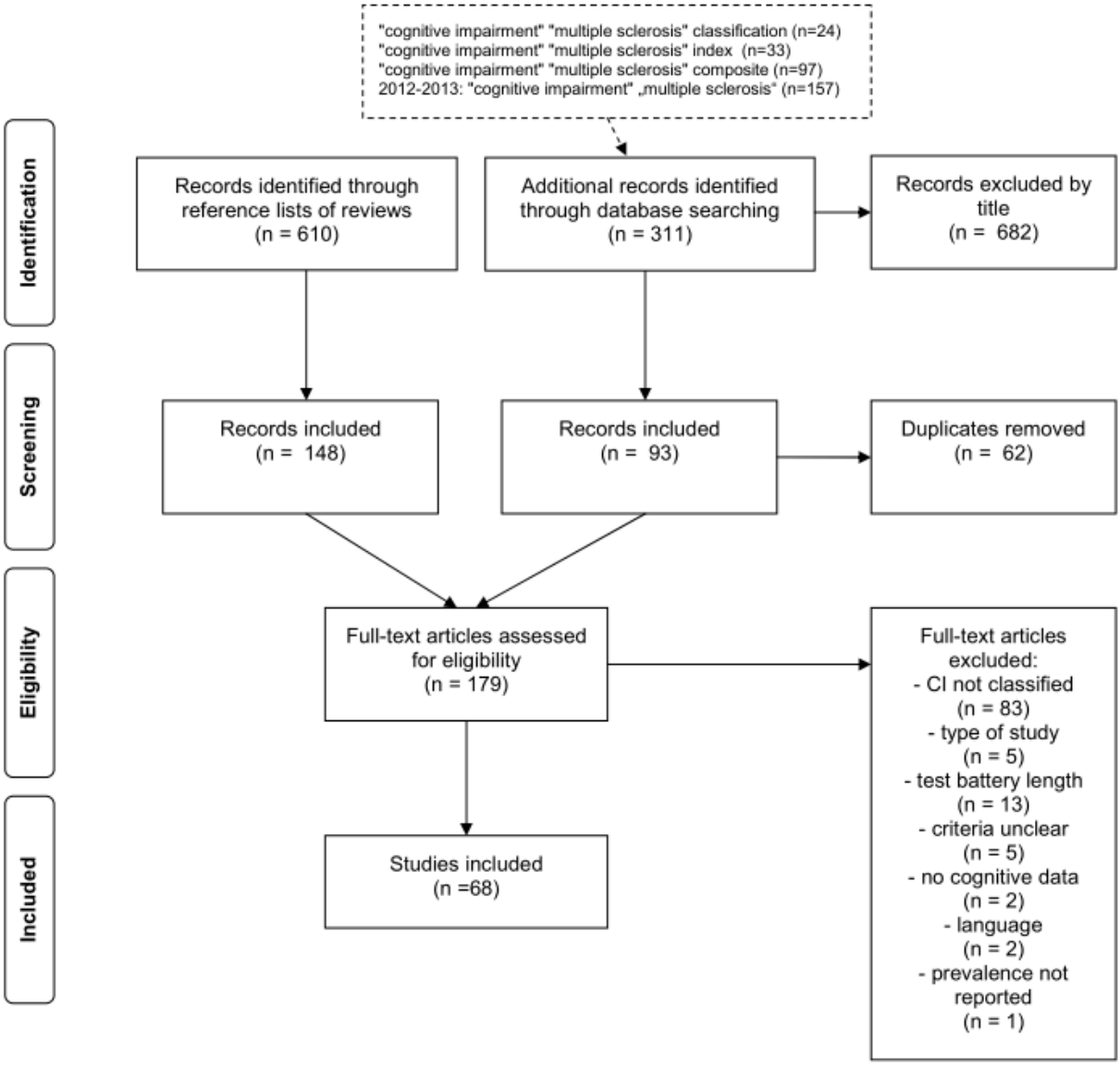

Figure 3. Flowchart of literature review

Table 2. Summary of the 70 reviewed classification criteria

n[1]	SD cut-off[2]	Criterion (stringency[3])	%CI[4]
Strategy 1: Critical number of abnormal parameters[5]			
18	2.0	abnormality in 24±11% parameters (conservative)	35±13
14	1.5	abnormality in 18±2% parameters (fair)	46±11
10	1.5	abnormality in 30±6% parameters (conservative)	40±12
3	2.0	abnormality in 17±11% parameters in at least two different cognitive domains	26±2
2	1.5	abnormality in 13% parameters (liberal)	48±2
2	2.0	abnormality in 6% parameters (liberal)	51±7
2	1.5 & 2.0	15% parameters ≥ 2 SD and 15% parameters ≥ 1.5 SD; or 44% parameters ≥ 1.5 SD	50±14
2	1.5	20% of tests abnormal (i.e. abnormality in 1 parameter of each test)	52±11
1	1.0	abnormality in 30% parameters (fair)	22
1	1.0	abnormality in 17% parameters (liberal)	94
1	2.0	abnormality in 8% parameters (fair)	29
1	1.5	abnormality in 13% parameters in at least two of the four main functional areas (psychomotor speed, attention, memory, executive function)	48
Strategy 2: Composite score[5]			
2	1.5	abnormal average of normalized parameters	15±13
2	1.5	abnormality in 25-29% cognitive domain scores (average of associated normalized parameters)	31±18
1	1.0	abnormal average of normalized parameters	28
1	1.5	abnormal graded sum (grading system for each parameter: 1-2 SD below normative mean [=1], more than 2 SD [=2])	40
1	1.5	abnormal sum of those normalized parameters that highly intercorrelate [Cronbach alpha=.76] and have a mean below T=50)	45
1	0.5 & 1.0	abnormal average of normalized parameters (0.5 SD) and one out of three cognitive factor scores (based on factor analysis) abnormally (1 SD)	38
Strategy 3: Combined criteria[5]			
2	1.5 & 2.0	average of parameters believed to be most sensitive to CI in MS (i.e., SDMT, PASAT, BVMT, and CVLT; cut-off 1.5 SD); or 10% parameters (2 SD) and 20% parameters (1.5 SD), or 20% parameters (2 SD) across all parameters	42±9
1	0.33 & 2.0	sum of normalized parameters (0.33 SD); or abnormality in 33% parameters (2 SD)	67

1: Number of associated criteria

2: "1.5 SD" includes also cut-offs based on the 5th percentile

3: When possible the criteria were classified in respect of their stringency (liberal, fair, or conservative). This was based on false positive rates, i.e., on how many parameters healthy people fail on a cut-off of 1, 1.5, and 2 SD[10]. Criteria were considered fair if CI was defined as performance below 1 SD on 32%±6.4%, on less than 25.6% as liberal, and on more than 38.4% as conservative. The respective figures were 17±3.4% for the 1.5 SD / 5th percentile cut-off, and 7.5±1.5% for the 2 SD cut-off

4: Percentage of cognitive impairment revealed in the reviewed papers utilizing the associated classification criterion (mean±SD)

5: Classification can be based on (1) the number of abnormal test parameters, (2) on the formation of a composite index, or (3) on a combination of the first two

Classification strategy and CI

Across all reviewed papers, an average of 41 ± 15% (range: 6 – 94 %) of patients were classified as cognitively impaired (**Table 2**). Criteria based on Strategy 1 reported a prevalence of 42 ± 15 %. Papers utilizing Strategy 2 reported CI in 30 ± 14 % and papers utilizing Strategy 3 reported CI in 50 ± 16 %. The differences in the impairment rate were not statistically significant ($F(2,69) = 2.85$, $p = .07$).

Stringency and CI

Stringency had an effect on impairment rate ($F(2,50) = 5.52$, $p < .01$). Prevalence rates were higher following liberal (58 ± 20 %) compared to conservative criteria (37 ± 13 %, $p < .01$). There was no difference between fair (44 ± 13 %) and liberal criteria ($p = .13$), and between fair and conservative criteria ($p = .22$). The continuous stringency measure correlated with percentage of impairment ($N = 51$, $r = -43$, $p < .01$).

Stringency and disease duration

Stringency had an effect on disease duration ($F(2,43) = 6.37$, $p < .01$). Disease duration was higher in conservative (11.2 ± 7.1 years) compared to liberal (2.4 ± 4.3 years, $p < .05$) and fair (6.0 ± 4.0 years, $p < .05$) criteria. There was no difference between the liberal and fair criteria ($p = .49$). The continuous stringency measure correlated with disease duration ($N = 44$, $r = .48$, $p < .01$).

2.3.2. New Data

Disease stage and CI

When applying the 20 classification criteria on our test battery and subjects (**Table 3**), we found a group effect on cognitive impairment ($F(3,80) = 3316.28$, $p < .0001$) with a higher prevalence in late (40 ± 18 %, range: 4 – 81 %) compared to early (12 ± 17 %, range: 0 – 68 %, $p < .0001$), control early (5 ± 10 %, range: 0 – 44 %, $p < .0001$), and control late MS (9 ± 15 %, range: 0 – 64 %, $p < .0001$). There were no differences between the other groups (all $p > .4$).

Classification strategy and CI

Strategy had an effect on impairment rate ($F(2,80) = 894.73$, $p < .05$). The prevalence derived from criteria associated to Strategy 1 (20 ± 22 %) was higher compared to Strategy 2 (9 ± 15 %), $p < .05$). There were no differences between Strategy 1 and Strategy 3 (19 ± 20 %, $p = .99$), and Strategy 2 and Strategy 3 ($p = .27$).

Classification criteria and CI in patients vs. controls

18 out of 20 criteria resulted in higher rates in late MS versus matched controls, whereas only 2 did so in early MS versus matched controls (**Table 3**). The prevalence rates, according to 16 criteria, were lower in early compared to late MS.

Table 3. Common classification criteria for cognitive impairment applied on own data of 77 MS patients and 75 matched controls: Prevalence rate of cognitive impairment.

SD Cut-off[1]	Criterion (stringency)[2]	Exemplary publication	% cognitive impairment					
			early stage[3]			late stage[4]		
			MS	control group	p[5]	MS	control group	p[5]
Strategy 1: Critical number of abnormal parameters								
1	abnormality in 13% parameters (liberal)	(Achiron & Barak, 2003)	68%	44%	.15	81%	64%	.08
	abnormality in 33% parameters (fair)	(Patti et al., 2009)	0%	4%	1	46%	6%	**.0001**
1.5	abnormality in 13% parameters (liberal)	(Glanz et al., 2007)	32%	4%	**.02**	58%	22%	**.0001**
	abnormality in 20% parameters (fair)	(Nocentini et al., 2006)	8%	0%	.49	46%	8%	**.0001**
	abnormality in 33% parameters (conservative)	(Amato et al., 2006)	0%	0%	N/A	21%	2%	**.001**
	abnormality in 13% parameters in at least two of the three main functional areas (attention, memory, executive function)	(Smestad et al., 2010)	20%	4%	.19	44%	6%	**.0001**
	25% of tests abnormal (i.e. abnormality in 1 parameter of each test)	(Deloire et al., 2006)	28%	4%	**.05**	62%	18%	**.0001**
2	abnormality in 6.7% parameters (liberal)	(Faiss et al., 2014)	36%	16%	.20	54%	16%	**.0001**
	abnormality in 13% parameters (conservative)	(Feuillet et al., 2007)	4%	0%	1	35%	2%	**.0001**
	abnormality in 20% parameters (conservative)	(Zipoli et al., 2010)	0%	0%	N/A	21%	0%	**.001**
	abnormality in 20% parameters in at least two different cognitive domains	(Zivadinov, De Masi, et al., 2001)	4%	0%	1	25%	0%	**.0001**
	abnormality in 13% parameters (≥ 2 SD) and in 13% parameters (≥ 1.5 SD); or in 40% parameters (≥ 1.5 SD)	(Benedict, Bruce, et al., 2006)	4%	0%	1	35%	2%	**.0001**

Strategy 2: Composite score								
com-po-site	average of normalized parameters (cut-off 1.0 SD)	(Achiron et al., 2013)	0%	0%	N/A	21%	0%	**.001**
	average of normalized parameters (cut-off 1.5 SD)	(Weinges-Evers et al., 2010)	0%	0%	N/A	4%	0%	.50
	abnormality in 25% cognitive domain scores (average of associated normalized parameters; cut-off 1.5 SD)[6]	(Khalil et al., 2011)	4%	0%	.49	33%	4%	**.0001**
	graded sum (grading system for each parameter: 1-2 SD below normative mean [=1], more than 2 SD [=2]) (cut-off 5th percentile of controls)	(Sánchez, Nieto, Barroso, Martín, & Hernández, 2008)	0%	0%	N/A	44%	2%	**.0001**
	average of normalized parameters (cut-off 0.5 SD) and one out of three cognitive factor scores (based on factor analysis[7]) (cut-off 1 SD)	(Denney, Lynch, & Parmenter, 2008)	4%	4%	1	31%	4%	**.0001**
	sum of those normalized parameters that highly intercorrelate [cronbach alpha=.76] and have a mean below T=50 (cut-off 1.5 SD on regression based residuals)	(Mathiesen et al., 2006)	8%	0%	.49	54%	10%	**.0001**
Strategy 3: Combined criteria								
comb-ined	sum of normalized parameters (cut-off 0.33 SD); or abnormality in 33% parameters (cut-off 2 SD)	(Lazeron et al., 2005)	12%	16%	1	58%	20%	**.0001**
	average of parameters believed to be most sensitive to CI in MS (i.e., alertness, divided attention, DCS, and AVLT; cut-off 1.5 SD); or 6.7% parameters (cut-off 2 SD) and 20% parameters (cut-off 1.5 SD), or 20% parameters (cut-off 2 SD) across all parameters[8]	(Benedict et al., 2004)	8%	0%	.49	37%	2%	**.0001**

1 "1.5 SD" includes also cut-offs based on the 5th percentile

2 stringency based on false positive rates (i.e., on how many parameters healthy people fail on a cut-off of 1, 1.5, and 2 SD (Schretlen et al., 2008)), the criteria were labeled as liberal, fair, or conservative (see methods for details).

3: disease duration < 2 years

4: disease duration >12 years

5: p-values of Fisher's exact test, testing for differences in prevalence rate in patients vs. controls

PP=Primary Progressive MS; TP= Transitional Progressive MS; SP=Secondary Progressive MS; RR=Relapsing Remitting; CIS=Clinically isolated syndrome

6: domain scores: (1) immediate recall: AVLT trial 1-5, DCS, VLT, NVLT; (2) delayed recall: AVLT difference trial 5 and delayed free recall, AVLT recognition, ROCF delayed receall; (3) mental processing speed: alertness, divided attention; (4) executive function: flexibility.

7: varimax rotated factor solution: (1) AVLT, VLT, DCS-storage; (2) alertness; (3) divided attention omissions, ROCF-recall, divided attention errors; (4) divided attention errors, divided attention RT; (5) DCS-learning, flexibility

8: DCS=Diagnosticum fuer Cerebralschaedigung, AVLT=Auditory Verbal Learning Test

Number of parameters below different SD cut-offs

To clarify whether very low, moderately low, or slightly low performances discriminate better between the groups of MS and controls, the number of performances that were 1 - 1.5 SD, 1.5 - 2 SD, and more than 2 SD below the normative mean were compared. All ranges of low performances as assessed by the aforementioned SD cut-offs increased in late MS compared to controls, whereas in early MS only a trend for very low performances could be revealed (**Table 4**).

Table 4. Number of parameters that are below different SD cut-offs

cut-off[a]	early stage					late stage				
	MS		control			MS		control		
	mean	SD	mean	SD	p[b]	mean	SD	mean	SD	p[b]
1-1.5 SD	0,92	0,76	1,20	1,04	0.39	2,08	1,41	1,12	1,08	0.001
1.5-2SD	0,64	0,76	0,32	0,48	0.14	1,40	1,49	0,70	1,04	0.011
>2SD	0,40	0,58	0,16	0,37	0.10	1,21	1,45	0,18	0,44	0.000

a: Number of parameters that were at least 1SD, but less than 1.5SD below the normative mean (1-1.5 SD), or at least 1.5SD, but less than 2 SD below the normative mean (1.5-2SD), or at least 2SD below the normative mean (>2SD)
b: p-values of Mann-Whitney Test

Inter-rater reliability of classification

The classification of all 20 criteria resulted in a moderate inter-rater reliability (Kendall's W [N = 20, df = 74] = 0.6, $p < 0.0001$). Similar inter-rater reliabilities were achieved within criteria of Strategy 1 (Kendall's W [N = 12, df = 74] = 0.6, $p < 0.0001$) and Strategy 2 (Kendall's W [N = 6, df = 74] = 0.6, $p < 0.0001$). On average 77 % (SD = 12, range: 25 - 100) of MS patients were classified the same by two separate criteria (**Table 5**). Classification of criteria with a comparable outcome (i.e., 4 criteria with 20 – 36 % CI in early MS; 4 criteria with 35 – 46 % CI in late MS), resulted in strong inter-rater reliabilities (Kendall's W [N = 4, df = 24] = 0.71; Kendall's W [N = 4, df = 51] = 0.84, both $p < .0001$). This means that in early MS 68 %, and in late MS 81 %, of patients were classified consistently across the four comparable criteria.

Table 5. Common classification criteria for cognitive impairment applied on own data of 77 MS patients: Inter-rater reliability (% of agreement between two separate criteria)

Criterion[1]		A	B	C	D	E**	F*	G	H	I	J*	K**	L	M	N*	O*	P	Q	R	S*	T*
	% CI[2]	76.62	50.65	49.35	48.05	42.86	38.96	36.36	33.77	31.17	29.87	27.27	24.68	24.68	24.00	22.08	18.18	14.29	14.29	14.29	2.63
A	76.62		74	73	66	66	62	60	57	55	53	51	48	48	43	45	42	38	38	38	25
B	50.65	74		96	74	82	81	86	83	78	77	77	71	71	69	71	68	64	64	64	51
C	49.35	73	96		75	81	73	82	84	79	78	79	75	77	71	66	69	65	65	66	53
D	48.05	66	74	75		71	73	70	73	75	77	79	77	77	64	66	70	66	66	66	54
E**	42.86	66	82	81	71		88	78	86	81	79	79	74	74	75	79	69	71	69	71	59
F*	38.96	62	81	82	73	88		77	87	87	86	83	78	78	76	78	75	75	75	75	63
G	36.36	60	86	82	70	78	77		79	82	83	78	78	78	73	75	82	75	75	75	66
H	33.77	57	83	84	73	86	87	79		90	88	94	86	86	87	83	82	81	81	81	68
I	31.17	55	78	79	75	81	87	82	90		99	88	91	91	87	83	84	83	83	83	71
J*	29.87	53	77	78	77	79	86	83	88	99		90	92	92	88	82	86	84	84	84	72
K**	27.27	51	77	78	79	79	83	78	94	88	90		92	92	85	84	87	87	87	87	75
L	24.68	48	71	75	77	74	78	78	86	91	92	92		100	88	87	91	90	90	90	78
M	24.68	48	71	75	77	74	78	78	86	91	92	92	100		88	87	90	90	90	90	78
N*	24.00	43	69	71	64	75	76	73	87	87	88	85	88	88		80	81	88	88	91	79
O*	22.08	45	71	70	66	79	78	75	83	83	82	84	87	87	80		82	90	82	87	80
P	18.18	42	68	69	70	73	74	82	82	84	86	88	91	91	81	86		91	91	88	84
Q	14.29	43	69	70	69	71	75	78	86	88	90	87	92	90	93	90	88		92	95	83
R	14.29	38	64	65	66	69	75	75	81	83	84	87	90	90	88	82	91	90		92	88
S*	14.29	38	64	65	66	71	75	75	81	83	84	87	90	90	91	87	92	95	92		88
T*	2.63	25	51	53	54	59	63	66	68	71	72	75	78	78	79	80	84	88	88	88	
	mean	51.9	74.0	74.8	70.7	75.6	77.3	76.6	82.1	82.9	83.2	82.9	83.0	82.9	79.2	78.6	79.6	79.5	78.9	79.5	69.2

1: Criterion is either based on a critical number of abnormal parameters (strategy 1), or on the formation of composite scores ("*"; strategy 2), or on a combination of composite scores and critical number of abnormal parameters ("**"; strategy 3): [A] abnormality in 13% parameters (cut-off 1SD); [B] 25% of tests abnormal (i.e. abnormality in 1 parameter of each test; cut-off 1.5SD); [C] abnormality in 13% parameters (cut-off 1.5 SD); [D] abnormality in 6.7% parameters (cut-off 2SD); [E] sum of normalized parameters (cut-off 0.33 SD); or abnormality in 33% parameters (cut-off 2 SD);[F] sum of those normalized parameters that highly intercorrelate [cronbach alpha=.76] and have a mean below T=50 (cut-off 1.5 SD on regression based residuals); [G] abnormality in 13% parameters in at least two of the three main functional areas (attention, memory, executive function, cut-off 1.5SD) ;[H] abnormality in 20% parameters (cut-off 1.5SD);[I] abnormality in 33% parameters (cut-off 1SD) ; [J] graded sum (grading system for each parameter: 1-2 SD below normative mean [=1], more than 2 SD [=2]) (cut-off 5th percentile of controls); [K] average of parameters believed to be most sensitive to CI in MS (i.e., alertness, divided attention, DCS, and AVLT; cut-off 1.5 SD); or 6.7% parameters (cut-off 2 SD) and 20% parameters (cut-off 1.5 SD), or 20% parameters (cut-off 2 SD) across all parameters; [L] abnormality in 13% parameters (cut-off 2 SD); [M] abnormality in 13% parameters (≥ 2 SD) and in 13% parameters (≥ 1.5 SD); or in 40% parameters (≥ 1.5 SD); [N] abnormality in 25% cognitive domain scores (average of associated normalized parameters; cut-off 1.5 SD); [O] average of normalized parameters (cut-off 0.5 SD) and one out of three cognitive factor scores (based on factor analysis) (cut-off 1 SD); [P] abnormality in 20% parameters in at least two different cognitive domains (cut-off 2 SD); [Q] abnormality in 33% parameters (cut-off 1.5 SD); [R] abnormality in 20% parameters (cut-off 2SD); [S] average of normalized parameters (cut-off 1.0 SD); [T] average of normalized parameters (cut-off 1.5 SD).

2: Criteria are sorted by percentage of cognitive impairment revealed by each criterion.

Inter-rater reliability between Strategy 1 and Strategy 2

The six criteria utilizing composite indices differed in their agreement with classification based on criteria of strategy 1 ($F(5,55) = 350.57$, $p < .0001$). The graded sum approach (Sánchez et al., 2008) showed the highest agreement (83 ± 3 %), whereas the approach based on a 1.5 SD cut-off of the averaged normalized parameters (Weinges-Evers et al., 2010) showed the least agreement (66 ± 5 %).

2.4. Discussion

The present study was driven by the question of how reliable the classification of cognitive impairment in MS is across common criteria. First, a review of classification criteria used by different researchers was provided. Then the different approaches were applied to the neuropsychological data of early and late MS patients and the outcome compared in terms of prevalence rate and inter-rater reliability.

The review revealed 20 distinct approaches that have been used to classify cognitive impairment in MS. They can be subdivided into three strategies. The first strategy is based on the number of abnormal test parameters, the second on the formation of a composite index, and the third is a combination of the first two. The majority of researchers utilize the first strategy but with differences in the cut-off for abnormal performance and in the critical number of abnormal performances. Thus, in spite of the suggested criteria of a fifth percentile cut-off on about 20 % of tests or test parameters (Benedict, 2009), a range of other criteria are still in use.

On average, the reported prevalences confirm the popular figure of 40% (Rao et al., 1991) but, as expected, studies utilizing more liberal criteria report higher prevalence rates than those with fair or conservative criteria. Moreover, our data shows that liberal criteria are more frequently utilized in samples with shorter disease durations. This bias makes it difficult to compare results on CI in early and late disease stages. It also suggests that CI may be overemphasized in the early disease stage. However, more than half of the 70 reviewed criteria applied a fair or conservative stringency on 1.5 or 2 SD cut-offs.

Combined criteria and criteria based on composite scores are rarely used. There is no consensus on how to define a composite score and we found variations from a simple average of all cognitive test parameters to factor analysis based solutions. As shown before, studies that took averaged standard scores as a composite find low rates of cognitive impairment (Olazarán et al., 2009), whereas the outcome of a composite score based on a grading system of failed parameters (Camp et al., 1999; Sánchez et al., 2008) is more comparable.

The sample of late MS patients demonstrated the profound effect that the choice of classification strategy has on the prevalence rate of cognitive impairment. Adopting the set of previously published criteria we found between 4 % and 81 % impaired patients. This result further challenges the reliability of the concept of cognitive impairment. The situation is complicated by the fact that, except for the very conservative or liberal ones, most strategies' outcomes differentiate between patients and controls.

Interestingly, no particular cut-off seems to be beneficial, which is due to the fact that the cut-off alone does not determine the prevalence rate, but rather the cut-off in combination with the required number of parameters below that cut-off (Schretlen et al., 2008). Using criteria in which the number and cut-off are adjusted at a similar level, we found significant statistical agreement across different cut-offs, i.e. more than two third of the patients are classified consistently. From this point of view, it is acceptable to use any of the three cut-offs, as long the number of critical parameters is adjusted. For this adjustment, this study confirms previously published data (Schretlen et al., 2008), i.e., that out of all parameters in a test battery at least 32 % should fall below 1 SD, 17 % below 1.5 SD, and 7.5 % below 2 SD, because then patients are well distinguished from controls and prevalence rates are comparable to the literature.

In the new data we could confirm that criteria that are based on composite scores result in lower rates of CI compared to criteria that are based on abnormality of parameters. This primarily applies to criteria that utilize an average of all standard scores (e.g., mean z). However, applying a very liberal cut-off (0.5 SD) on this average, leads to a classification agreement of 90 % with the common 1.5 SD cut-off on 20 % parameters (ROC analysis: area under the curve = .97, data not shown). This shows that the mean of standard scores is a

reliable alternative in classifying cognitively impaired patients. Other reliable alternatives are the compound measure defined as a graded system first introduced by Camp and colleagues (Camp et al., 1999; Sánchez et al., 2008), and the regression-based approach by Mathiesen and colleagues (2006).

The findings in the early disease stage are less straightforward. As in the late stage, the impact of the utilized classification strategy is considerably high (rates from 0 % to 88 %). However, less than 10 % of patients were cognitively impaired following fair and conservative criteria on either cut-off, as well as composite scores, suggesting that these strategies are too stringent to investigate early cognitive impairment in MS. By using more liberal criteria, the rates can be increased, but - except for the 1.5 SD cut-off - they do not distinguish from false positive rates in healthy controls. Moreover, the effect of the liberal 1.5 SD criterion was primarily due to the extraordinary performance of controls for early MS that failed 5 times fewer on this criterion than controls for late MS. Compared to a more representative control group of early and late controls, only the liberal 2 SD criterion might reveal increased prevalence in early patients ($p = .08$, data not shown). Thus, whereas the 1.5 and 2 SD cut-offs in liberal criteria are to some extent specific and concordant, the 1 SD cut-off is not, no matter how stringently it is handled. Accordingly, our data suggests that patients in the early stage are characterised by an increase in very low performances (> 2 SD) rather than by an increased number of borderline or slightly abnormal performances.

The data on inter-rater reliability suggests that a high agreement in classification of CI in MS can be achieved with very different classification strategies. It seems far more important to correct for false positives, especially in respect of multiple comparison errors in larger test batteries. This can be done by employing a control group. Alternatively, the aforementioned adjustments for different SD cut-offs can also be used to calculate cut-offs on composite scores. For example, the fifth percentile cut-off on 20 % parameters equals a mean z of -0.3. Altogether, the data indicates that the stringency is the key factor in classifying CI in MS that needs to be better homogenized between future studies. An additional differentiation of cognitive impairment into mild, moderate, and severe forms based on the aforementioned criteria can facilitate comparability (Amato et al., 2001).

The impact of methodology we found on the classification of cognitive impairment in MS complements the work of Walker and colleagues (2011), who reported similar findings on interpretation of longitudinal cognitive data. The present results are also in line with research on the classification of mild cognitive impairment (MCI) in geriatric patients. Here, a similar high prevalence range between common criteria has been reported (i.e., 9 % to 74 %) (Jak & Bondi, 2009). Additionally, as supported by the findings of this paper, a good correspondence of classification in two out of three patients occurs if two criteria lead to comparable prevalence rates. Remarkably, conservative strategies seem to be more reliable, based on a better longitudinal stability and significant associations with external markers (e.g., medial temporal atrophy) (Schinka & Loewenstein, 2010). Accordingly, only the conservative criterion in Zipoli et al.'s study (Zipoli et al., 2010) (i.e., 30 % abnormal parameters below a 2 SD cut-off) had predictive value for conversion from CIS to MS.

The present study suggests that some of the reported prevalence rates of cognitive impairment in early disease stages could be overestimated due to the usage of liberal criteria (Achiron & Barak, 2003; Deloire et al., 2006; Glanz et al., 2007). It, therefore, helps to explain differences, as in Weinges-Evers et al. (2010) who only found 6 % and Deloire and colleagues (2006) who found 60 % of patients cognitively impaired in two comparable samples of early MS patients. Applying their classification criteria on our data contrasts rates of 0 % and 28 %.

The main limitation of our study is the small sample size of the early MS group. Compared to other studies, we recruited a sample in which most patients appeared cognitively preserved. Following the more stringent criteria, we could detect impairment in neither the early MS nor the control group and therefore cannot exclude the possibility that our sample contained no one suffering from cognitive impairment. A recent study is in line with that notion, showing early impairment only in verbal fluency, but not in working and verbal episodic memory, flexibility, and information processing speed (Brissart, Morele, Baumann, & Debouverie, 2012). Although our recruitment was mostly unbiased (subjects chosen by demographic criteria to match with late MS patients and not by probable cognitive impairment), we did exclude patients with severe depression or fatigue, both of which are associated with cognitive impairment (Patti, 2009). Even though depression and fatigue are

prevalent in MS, the cut-offs used in this study were considerably higher than usual (CES-D: 39 compared to 23, WEIMUS: 32 compared to 52) and only two patients had to be excluded due to fatigue. Our test battery assessed executive functions as part of complex tests, but not specifically those aspects that are typically impaired in MS, i.e., verbal fluency or card sorting. However, executive deficits are rare in early stages (Henry & Beatty, 2006) and the inclusion of those tests should not have had much effect on prevalence rates.

It is also important to keep in mind that only one of many factors that contribute to impairment classification in neuropsychological practice was investigated. Usually, test performance is evaluated under consideration of other factors such as pre-morbid cognitive performance, motivational factors, behavioural observations, external information from friends and relatives, and overall coherence. However, these factors are hardly part of studies on cognitive impairment.

The impact of cognitive impairment on daily function based on different criteria remains undetermined. For example, it is likely that liberal criteria classify some patients as cognitively impaired who are not affected by it in their social, occupational, and psychological functioning. In fact, in more subtle cases the ecological validity of CI classification is the major problem. However, there are no reliable measures of ecological validity available and perceived cognitive deficits are often associated with depression (Benedict et al., 2004). Also, even though cognitive impairment in MS further deteriorates (Amato et al., 2001), it is unclear whether the same holds true for CI based on liberal criteria in early MS stages, i.e., is the classification stable over time and does it have predictive value for further cognitive deterioration?

In conclusion, the high prevalence range between common classification strategies is primarily the result of differences on the liberal to conservative stringency axis. In contrast, conceptually different classification criteria, such as composite index vs. multiple tests, domain-specific vs. domain-unspecific and high vs. low SD cut-off, provide concordant classifications. Nonetheless, in early disease stages, in which relatively well preserved cognitive functions can be expected, strategies that rely on a liberal stringency and higher SD cut-offs provide sufficiently large percentages of impaired patients. It is important to note that these are with uncertain significance due to false positives. Here, data from a matched

control group should be acquired. In later stages, other criteria, including a composite index, are reliable alternatives to the common 1.5 SD cut-off on 20 % of tests or test parameters (Benedict, 2009). To avoid these classification issues, one could use current standardised test batteries for MS recommended by the international consortium, i.e., MACFIMS, BRB-N, BICAMS (Langdon et al., 2012).

3. Study two: Information processing deficits as a driving force for memory impairment in MS: A cross-sectional study of memory functions and MRI in early and late stage MS.

3.1. Introduction

Memory impairment (MI) can affect up to 65% of patients with multiple sclerosis (MS). In the past years it was found that significant MI can already be present in the first years after MS onset (Grant, McDonald, Trimble, Smith, & Reed, 1984; Schulz et al., 2006; Sicotte et al., 2008) and that structural (Koenig et al., 2014; Pardini et al., 2014; Planche et al., 2015; Sicotte et al., 2008) and functional alterations (Hulst et al., 2015) of the hippocampus correlate with the degree of MI.

However, several studies reported conflicting results demonstrating well preserved memory performance in the early MS stage (Kern et al., 2015; Nygaard et al., 2015; Panou, Mastorodemos, Papadaki, Simos, & Plaitakis, 2012; Pardini et al., 2014; Roosendaal et al., 2010), a lack of correlation between hippocampal alterations and MI (Anderson et al., 2010; Debernard et al., 2015; Kern et al., 2015; Roosendaal et al., 2010) or correlations with only some memory functions (Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Kiy et al., 2011). The reasons for these inconsistencies are not clear and hinder the understanding of the underlying mechanism of MI in MS.

One source of confound might be related to methodology. First, it is possible that the correlations between memory performance and MR-based parameters are confounded with disease stage. More specifically, the effect of focal damage on memory may be more pronounced in early stages, whereas in later stages the effect of global tissue loss plays a more important role (Planche et al., 2015; Schoonheim, Meijer, & Geurts, 2015). Secondly, MI could be confounded with slowed information-processing (IPS), which is a core deficit in MS and basic cognitive function affecting learning and memory (Costa, Genova, DeLuca, & Chiaravalloti, 2017). In other words, an association of MI with slowed IPS could provide an

alternative explanation to direct destructions in memory specific tracts such as the hippocampus (Sacco et al., 2015). Finally, the use of different test paradigms for memory assessment could have contributed to the heterogeneity of previous results (Anderson et al., 2010). In fact, as an alternative to the international standard screening tests of MS-related MI (i.e., SRT, SPART, BVMT-R, CVLT), locally validated memory assessments have been used (Longoni et al., 2015; Roosendaal et al., 2010; Schulz et al., 2006) as well as extensive memory test batteries (Anderson et al., 2010; Grant et al., 1984; Panou et al., 2012) and shorter screenings (Sicotte et al., 2008).

The present study was designed to evaluate MI in MS with an emphasis on the aforementioned methodological aspects, i.e., contrasting early and late disease stage, controlling for a potential IPS deficit, and utilizing multiple memory test paradigms. In a first step MI was assessed in individually matched patients with early versus late MS by using five memory tests and including an individually matched healthy control group. MI was discriminated from performance in three tests constituting IPS. In a second step the correlations with MRI were evaluated at both disease stages including T1/T2 lesion load, hippocampus volume, brain volume, and cortical thickness.

3.2. Methods

The present paper reports results of a multi-center, cross-sectional study that was designed to compare visual processing capacity, cognitive functions and associated MRI markers in early versus late MS. Memory was the cognitive function of primary interest in this study and therefore a key element of the study design was the implementation of five different tests of episodic memory. Also, the study included patients with disease durations of either less than 2 years or more than 12 years in order to contrast MI emerging from very early MS-related effects and MI emerging from later deterioration (Amato et al., 2001). To control for possible confounders, patients were recruited as individual pairs matched for age at disease onset, gender, and education.

The study was approved by the Ethical Committee of the Saechsische Landesaerztekammer (EK-BR-24/10-1) and all subjects provided written informed consent prior to participation.

Subjects

Seventy-seven patients (**Table 6**) diagnosed with clinically isolated syndrome, RRMS, or SPMS (Polman et al., 2005) were recruited in five MS centres in Germany (Wermsdorf, Halle, Magdeburg, Rostock, Teupitz) between February and September 2011 and assigned to two matched groups, one group with disease duration less than 2 years from the first clinical event (EMS) and another group with disease duration longer than 12 years (LMS). Patients were individually matched with respect to age at disease onset (+/-3 years), gender and education, i.e., after inclusion of one EMS-patient, two matching LMS-patients were recruited. More LMS-patients were recruited to account for the higher variety of structural and cognitive changes at later disease stages. Each site was instructed to recruit sets of 3 matched patients. For this purpose, outpatients were consecutively screened at each site for potential eligibility and matching. When a set was identified, the corresponding patients were invited for inclusion. However, if a site was not able to recruit a full set, the patients' characteristics were entered into a centralized recruitment spread sheet and the other sites were given the opportunity to recruit matching patients to the set.

Exclusion criteria were a relapse or corticosteroid treatment 4 weeks prior to neuropsychological assessment, visual acuity <0.2, severe fatigue (Wuerzburger Fatigue Inventory for MS ≥52 (Flachenecker et al., 2006)) or depression (Center for Epidemiological Studies Depression Scale ≥39 (Hautzinger & Bailer, 1993)), alcohol abuse, pregnancy, other relevant serious neurological and internal medical diseases as well as exclusion criteria for MRI.

Additionally, 75 individually matched healthy control subjects were recruited by the MS centres mentioned above and a sixth centre in Jena, Germany with corresponding age (+/-3 years), gender and education and assigned to two control groups (cEMS, cLMS). The same exclusion criteria were applied. All subjects received financial compensation for their travel expenses.

Table 6. Clinical and demographic variables.

	MS		controls		p[a]		
	EMS	LMS	cEMS	cLMS	EMS vs. LMS	EMS vs. cEMS	LMS vs. cLMS
N	25	52	25	50			
Sex (m/f)	8/17	16/36	8/17	14/36	1	1	,830
Age (years, mean±SD)	29,2±6,7	45,3±7,8	28,6±7,3	44,4±7,7	**,000**	,734	,591
Age at disease onset (years, mean±SD)	28.2±7.0	28.7±7.1			,777		
Disease duration (years, mean±SD)	1.0±0.8	16.5±5.2			**,000**		
Relapses past year (mean±SD)	1.5±1.9	0.3±0.7			**,000**		
Multifocal involvement at onset	24.0%	23.0%			1		
EDSS (Median [min-max])	2.0 [0-6]	3.3 [0-8]			**,000**		
Using MS medication	96.0%	88.5%			,257		
Education ≥12 years	36.0%	28.8%	36.0%	26.0%	,603	1	,830
Depression (CES-D, mean±SD)	12,8±9,7	13,0±9,2	7,4±4,7	8,8±8,2	,910	**,017**	**,017**
Fatigue (Weimus, mean±SD)	19,6±16,3	26,6±14,5	6,9±8,3	7,8±10,4	*,059*	**,001**	**,000**

a: p-values of independent samples t-test or Fisher's exact test (gender, education).
EDSS: Expanded Disability Status Scale; CES-D = Center for Epidemiologic Studies Depression Scale; Weimus = Wuerzburger Erschoepfungsinventar bei MS.

Neuropsychological Assessment

IPS and memory functions were assessed in a single 1.5h lasting session. To account for the multiple facets that can contribute to the IPS deficit in MS (Costa et al., 2017), three tests were applied assessing responsiveness for visual stimuli, divided attention for visual and auditory stimuli, and the ability to shift the attentional focus (Zimmermann & Fimm, 2011) (**Table 7**). Five standardized and validated memory tests were applied to assess verbal and visual memory (Helmstaedter et al., 2001; Strauss et al., 2006; Sturm & Willmes, 1999; Wolfram et al., 1989) (**Figure 4**). Tests were performed in the following fixed order: AVLT (learning), ROCF (copy), alertness, divided attention, flexibility, AVLT (recall, recognition), ROCF (recall), DCS, VLT, and NVLT.

Individual raw scores of patients and controls were converted to standard T-scores based on normative data of the corresponding test manuals correcting for age-, gender-, and education. To analyse correlations with MRI, patients' cognitive data was further corrected by calculating a z-score for each test: z = (patient's T-score - mean of the control group) / SD

of the control group. Impairment in each test was defined as a z-score < -1.5. Two or more impaired memory scores were considered to indicate MI. The z-scores of the tests constituting IPS were averaged into an IPS index score (IPS_z).

For comparison with the literature, performance in the most frequently used test of IPS in MS, the SDMT (Scherer, Baum, Bauer, Göhler, & Miltenburger, 2004), was analyzed in 62 patients (21 EMS, 41 LMS) who agreed to a follow-up assessment 4.25 years (Min = 3.75, Max = 5.0, SD = 0.23) after the original evaluation.

Table 7. Neuropsychological tests used to evaluate IPS.

Test[a]	**Cognitive domain of interest**	**Concept**	**Scores**
Alertness	Responsiveness	Reaction to a simple visual stimulus.	reaction time
Divided attention	Divided attention	Selective reaction to competing auditory and visual stimuli	reaction time auditory; reaction time visual; errors; omissions
Flexibility	Shifting attention mental flexibility	"Set-shifting" task that requires reactions to complementary visual target stimuli on an alternate basis from trial to trial	reaction time; errors

a: Test are part of a computerized test battery(Zimmermann & Fimm, 2011).
IPS: Information-processing speed.

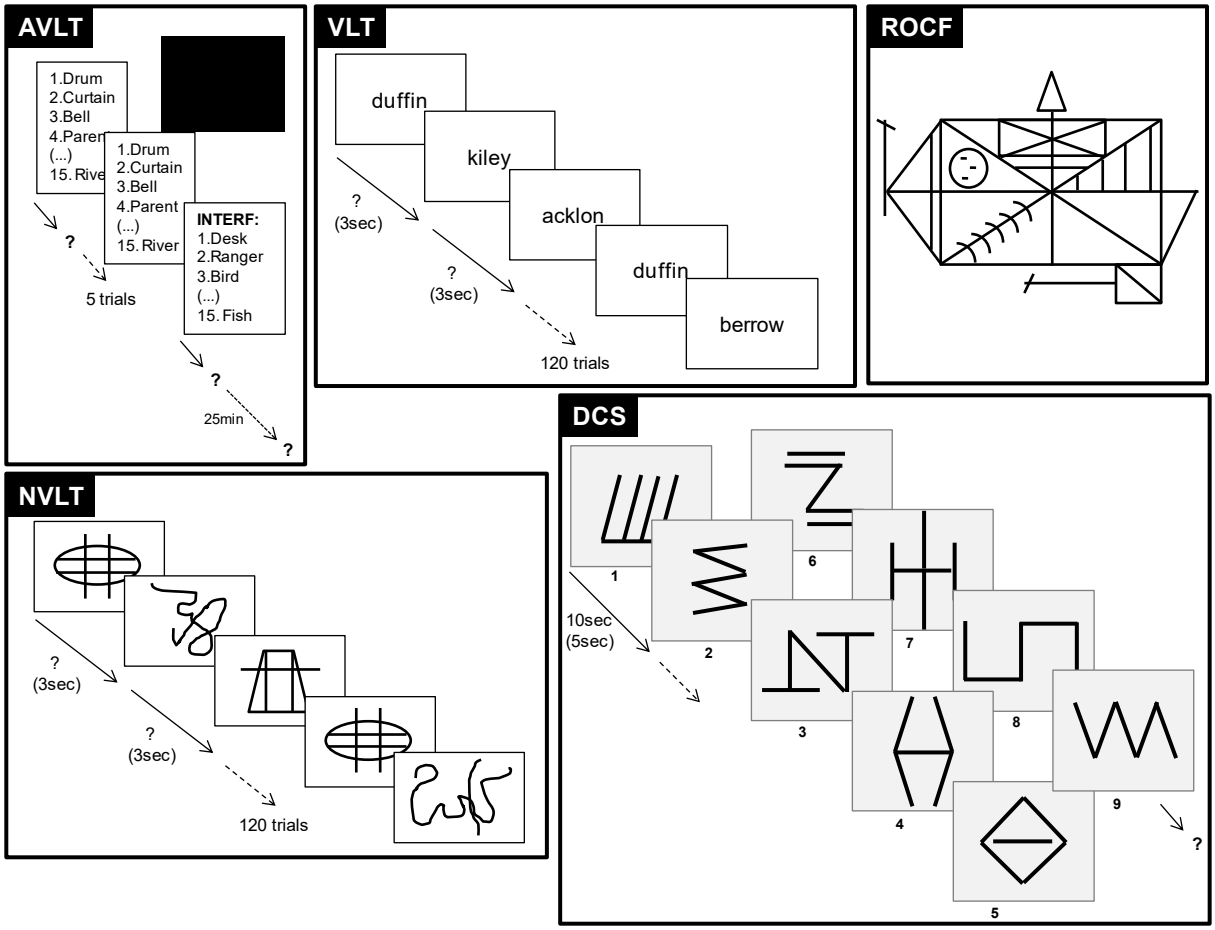

Figure 4. Schematic illustration of the five different memory test paradigms used.

Note: the displayed stimuli above resemble the original test material. Auditory Verbal Learning Test (AVLT): A list of 15 unrelated words is read aloud five times to the patient at the rate of one item per second. After each reading, patients are asked to recall all words they can remember in any order. The sum of correct answers is the learning index. After an interference trial with 15 other unrelated words, patients are asked to recall the first list again. Delayed recall (number of correct items) and recognition (differences of correct answers and false positives) of the first list is tested after a period of 20-25 minutes. Verbal Learning Test (VLT): In this recurring recognition test patients are presented 120 consecutive cards containing non-words at a rate of one card per 3 seconds. Eight of the first 20 non-words reappear in the course of the test, five times each. Patients are asked to memorize items and decide for each item if they recognize it from one of the previous cards or not. The difference between correct answers and false positives is scored as the learning index. Rey-Osterrieth-Complex-Figure-Test (ROCF): Patients are asked to copy a complex figure on an empty sheet. After a 20-25 minutes delay, patients are asked to reproduce the figure again from memory. There is no warning of the memory component at any point. Accuracy of reproduction is scored based on the Taylor Scoring System. Nonverbal Learning Test (NVLT): Designed as a parallel test to the VLT, the stimulus material consists of geometric and irregularly shaped figures instead of non-words. All other parts of the test are identical to the VLT. Diagnosticum For Cerebral Damage (DCS): Nine geometric figures are presented at a rate of 10 seconds per item. Patients are asked to memorize the exact spatial arrangement of each figure and the order they were presented at. After each presentation patients are asked to reconstruct as many items as possible in the correct order using five wooden sticks of equal length. Two more trials are followed with a slightly faster presentation time of 5 seconds per item. Scoring is based on errors, i.e., a correctly reconstructed item (shape and position) is scored zero error points; a missed or entirely incorrect item is scored seven points. Incomplete reproductions are scored one error point for each incorrectly placed stick and for incorrect orientation (twisted, mirrored); incorrect positioning is scored two error points. The retention index is an indicator of immediate memory and defined as the sum of errors in the first trial. The learning index is defined as: (errors trial 1 –errors trial 3) / (errors trial1 x 3) x 100.

Magnetic resonance imaging (MRI)

For standardization, all scans were audited with phantom and pilot subject scans on all sites at the beginning of the study. The MR parameters of the used sequences were optimized to get comparable T1- and T2-contrasts with the different scanners. Fourteen days before or after the neuropsychological assessment MRI data were acquired using one of the following systems: GE Sigma Horizon LX 1.5T neuro-optimized magnetic resonance system, Philips Intera 1,5T Master Nova, Siemens 1.5T Symphony, Siemens Avanto 1.5T neuro imaging magnetic resonance system, 3T Siemens Magnetom Vario scanner.

The MR protocol consisted of a T1-weighted sagittal 3D scan with a voxel size of 1.0 mm^3 to 1.5 mm^3. The proton density and T2-weighted scans were acquired as 3 mm axial slices aligned to the AC-PC line without a gap (TE = 12-30/90-120 ms, TR = 2800-4500 ms). In addition the MR protocol included a T1-weighted spin echo scan (TE < 25 ms, TR = 400-650 ms) after injection of gadolinium-DTPA (0.3 mmol/kg) in the same orientation as the T2 scan.

MRI was evaluated by independent and blinded technical staff members of the neuroimaging and neuroimmunology research group Magdeburg to obtain T1 lesion volume, T2 lesion volume, normalized hippocampus volume (NHV), normalized whole brain volume (NBV), and cortical thickness. The segmentation of lesions was performed on T1-weighted images with and without contrast agent and also on T2-weighted images using the DispImage package (Plummer, 1992). The volume of the stored region files were analyzed by using a calcroi tool. The contours of the hippocampus were traced on coronar slices using the software “MultiTracer” (Woods, 2003) following standardized guidelines (Pruessner et al., 2000) and stored as contour files in the ucf file format. Subsequently, the normalized hippocampus volumes were calculated with a self written matlab script using the ucf files and the head-normalization factor derived from SIENAX (Smith et al., 2002). The estimation of the total brain tissue volume from a single image and normalised skull size was performed using the software SIENAX (Smith et al., 2002) as part of FSL (Smith et al., 2004). Cortical reconstruction and volumetric segmentation was performed with Freesurfer 5.3 using recon-all for all subjects. Detailed descriptions of the methods are given elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999).

Statistical Analysis

Statistical analyses were performed with SPSS and by an independent biometrical institute using Statistical Analysis Systems (SAS 9.2). All analyses were restricted to subjects with complete data on all variables required for a particular analysis.

Group differences for demographic and clinical variables were tested by independent samples t-test or Fisher's exact test.

Group differences for IPS and memory were tested by using independent samples t-test. To control for the effect of IPS on memory performance, a multivariate GLM was computed including IPS_z as a covariate.

The SDMT performance was analyzed in each group separately. Additionally to the descriptive statistics, possible correlations to the IPS_z score at baseline were evaluated.

Group differences for MRI variables were assessed using independent samples t-test, or, if variables were not normally distributed (verified using the Kolmogorov–Smirnov Test), Mann-Whitney test.

Those memory scores that were found to be significantly lowered in patients compared to controls were further analysed in respect to correlations with the MRI data. First, partial correlations were computed with age and sex as covariates. Then, the relative contribution of MRI variables and IPS to the outcomes of the respective memory scores were analyzed by using stepwise regression analyses with the MRI parameters (values of T1/T2 lesion volumes were log-transformed in order to obtain a normal distribution) and IPS_z, as well as age, sex, depression and fatigue as predictor variables. As MRI variables were correlated, multicollinearity was checked with the tolerance factor (critical value of 0.2). The minimum significance level for entry and for staying in the equation was 0.05 and p = .1 to exit. A p-value < 0.05 was considered statistically significant.

3.3. Results

Three patients and two control subjects that were screened for inclusion were not included because of severe fatigue or depression scores. In total, 25 sets of matched patients (i.e., 1

EMS and 2 LMS) were recruited. 16 of these sets were recruited entirely by one site, another 5 sets were partially recruited by one site (i.e., 1 EMS and 1 LMS), and the remaining 4 sets were matched across three different sites (**Figure 5**). One patient withdrew his consent to participate after the MRI assessment (reasons unknown) and therefore no cognitive data was acquired. One patient could not perform three tests (divided attention, ROCF, DCS) because of severe spasms. Mental overload was the reason for one patient to not perform the tests of divided attention and NVLT and for another patient to dismiss auditory stimuli in the divided attention test. Data from the Flexibility test was missing for three patients and four control subjects because the incorrect test condition was applied. The baseline variables of the 152 included (**Table 6**) subjects show that matching for age at disease onset, education and gender was successful. EMS patients were younger and less disabled than LMS patients. Patients had higher depression and fatigue scores compared to controls.

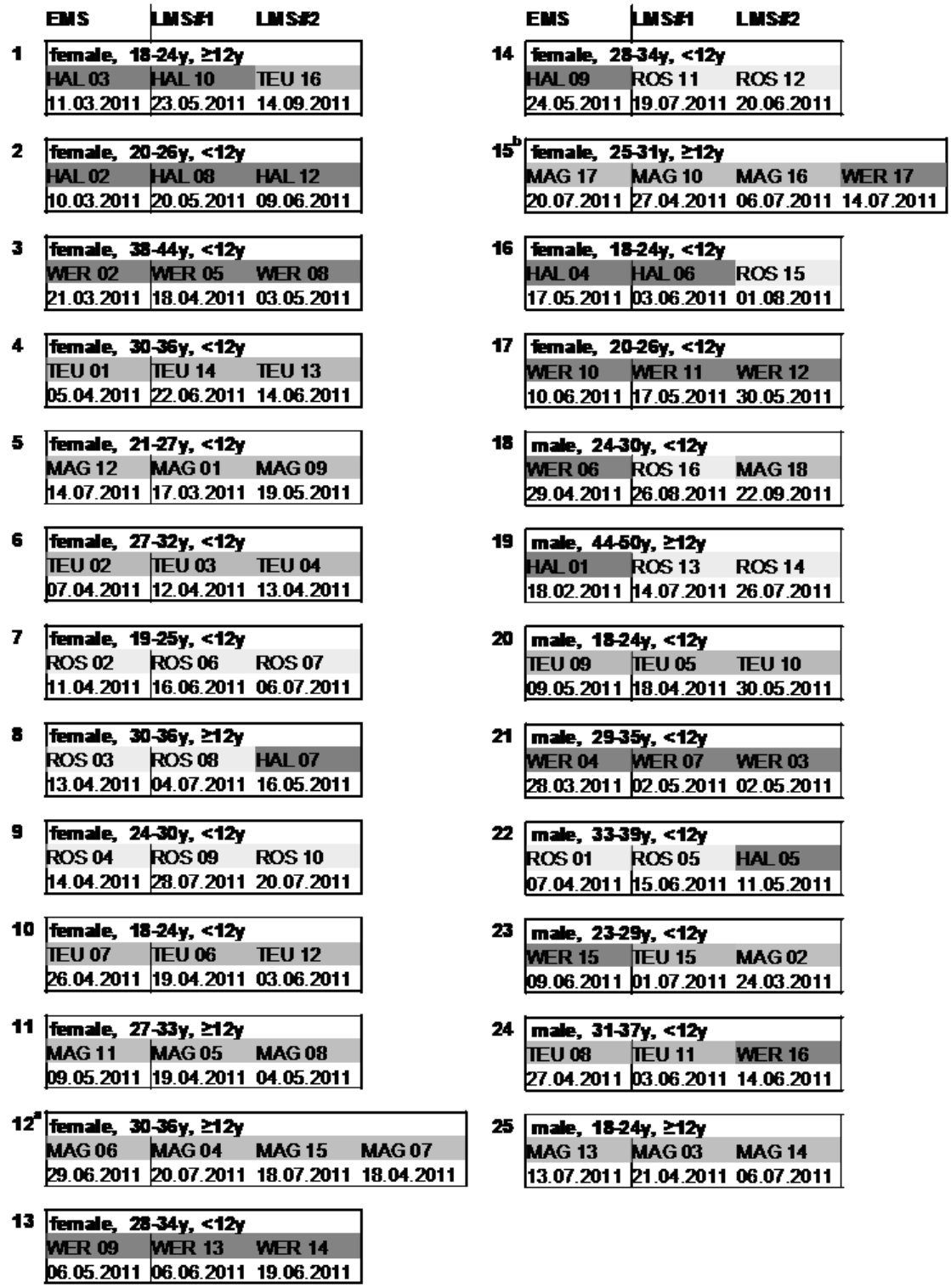

Figure 5. Recruitment and matching of the 77 included MS-patients.

Each box illustrates 1 of the 25 sets of 3 matched patients: One patient with early MS (EMS) was matched with 2 patients with late MS (LMS) in respect to sex, age at disease onset and education (the top row of each box indicates the corresponding matching criterion). The middle row illustrates at which site each patient was recruited and the local serial number (HAL = Halle, MAG = Magdeburg, ROS = Rostock, TEU = Teupitz, WER = Wermsdorf). The bottom row contains the actual inclusion dates. a = "MAG 07" was recruited as replacement for "MAG 04" who did not attend the first appointment, but was assessed later on; b = "MAG 10" withdrew her consent to participate in the study after the MRI and was replaced with "WER 17".

Neuropsychological performance

LMS

LMS patients performed significantly lower than controls in all aspects of IPS (**Table 8**). They were found to have a declined responsiveness, an increased number of missed stimuli under divided attention, as well as a slowed reaction time and increased number of errors in the test of mental flexibility.

The average impairment rate across all memory scores was 23 % (SD = 6) (minimum: 16 % in AVLT-learning; maximum: 34 % on DCS-learning; **Figure 6**). 43 % of LMS patients met the criterion for MI compared to 12 % in the control group ($p < .001$). Significant group effects were evident in the VLT, delayed recall of the AVLT, delayed recall of the ROCF, DCS-learning and NVLT (**Table 8**). However, IPS_z was found to be correlated with performances in the AVLT, ROCF, and DCS (**Table 9**). After controlling for IPS_z, only the difference in the VLT remained to be significant (**Table 8**).

The average number of correct answers in the SDMT at follow-up was 46.58 (SD=13.0) which was below the norm ($M_{T\text{-values}} = 44.36$, SD = 12.5, Min = 16, Max = 69). SDMT and IPS_z were found to be strongly correlated ($r = .724$, $p < .001$).

EMS

In contrast, only 12 % of EMS patients met the criterion for MI which was within the normal range (cEMS: 16 % MI, $p = 1$). The average impairment rate across all memory scores was 10 % (SD = 7) and also did not exceed the one of the control group (10 %, SD = 5). Group effects were found in the VLT (EMS < cEMS) and AVLT-recognition (EMS > cEMS). Adding IPS as a covariate did not change the results (**Table 8**).

The average number of correct answers in the SDMT at follow-up was 60.65 (SD = 7.4), which was slightly above the norm ($M_{T\text{-values}} = 52.26$, SD = 7.3, Min = 38.5, Max = 68). No significant correlation was found between SDMT and IPS_z ($r = .22$, $p = .350$).

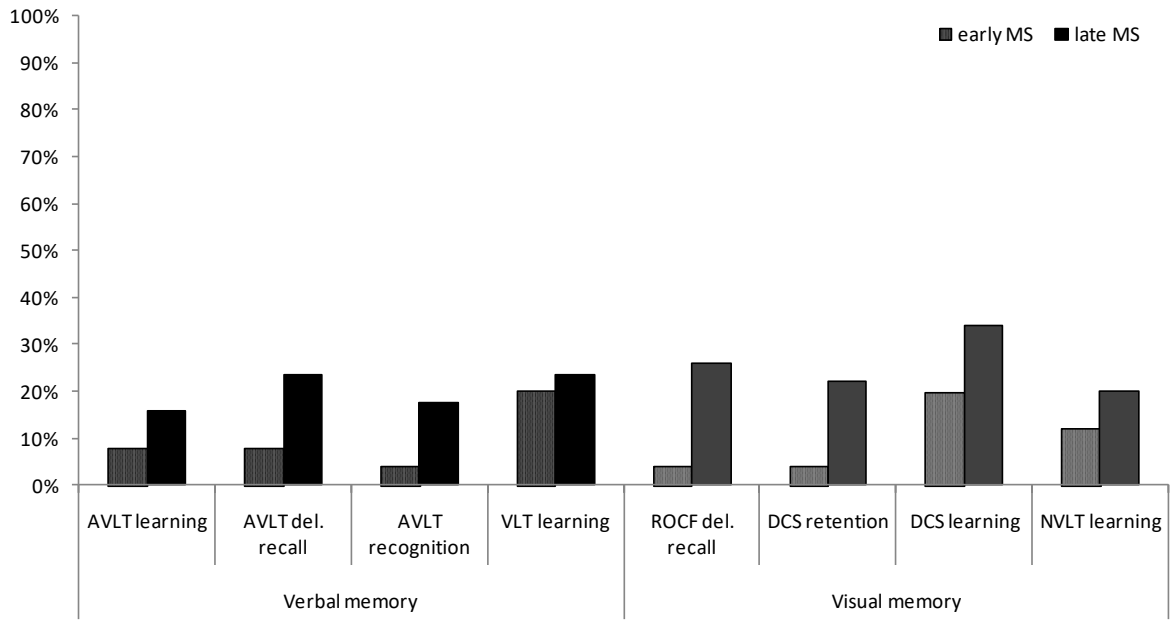

Figure 6. Impairment across different memory tests in patients with early and late MS.

Cut-off for impairment was a standardized performance (according to the corresponding test manual) that fell 1.5 SD below the average of the individually matched control group. Early MS = MS Patients with disease duration < 2 years. Late MS = MS Patients with disease duration > 12 years. *AVLT = Auditory Verbal Learning Test. ROCF = Rey-Osterrieth-Complex-Figure. DCS = Diagnosticum For Cerebral Damage. VLT = Verbal Learning Test. NVLT = Nonverbal Learning Test.*

Table 8. Results of neuropsychological assessment in MS patients with a short versus long disease duration, and matched controls.

Neuropsychological Outcome		Early MS						Late MS					
		patients (I)		controls (II)		p-value		patients (III)		controls (IV)		p-value	
Test	Score	N	T-value[a]	N	T-value[a]	T-Test[b]	GLM with IPS as covariate[c]	N	T-value[a]	N	T-value[a]	T-Test[b]	GLM with IPS as covariate[c]
Information-processing speed													
Responsive-ness	RT	25	47,4±9,0	25	46,9±6,2	,826		51	42,7±10,0	50	47,4±7,5	**,009**	
Divided attention	vis. RT	25	51,0±6,2	25	51,2±6,4	,911		49	45,9±10,2	50	51,1±7,8	**,005**	
	aud. RT	25	45,7±10,9	25	45,8±7,5	,976		48	41,0±9,7	50	46,9±8,6	**,002**	
	errors	25	48,8±5,6	25	46,1±8,3	,193		49	44,3±9,8	50	45,6±9,7	,524	
	omissions	25	51,6±5,4	25	48,7±6,8	*,096*		49	43,7±10,9	50	48,5±8,5	**,017**	
Flexibility	RT	23	54,8±8,4	25	53,3±7,6	,507		50	48,3±11,0	46	55,5±6,5	**,000**	
	errors	23	55,5±6,0	25	55,4±6,4	,964		50	50,8±10,6	46	57,3±5,9	**,000**	
Verbal memory													
AVLT	learning	25	55,1±8,8	25	55,0±8,5	,974	,862	51	53,4±8,9	50	55,8±8,3	,169	,864
	del. recall	25	52,2±8,3	25	54,5±9,8	,379	,393	51	48,0±8,6	50	52,8±7,4	**,003**	,151
	recognition	25	52,1±2,2	25	50,3±3,5	**,042**	**,049**	51	49,4±6,5	50	51,7±5,7	*,056*	,220
VLT	learning	25	45,7±8,7	25	51,0±7,5	**,026**	**,035**	51	44,4±10,5	50	49,5±9,9	**,014**	**,028**
Visual memory													
ROCF	del. recall	25	54,1±6,6	25	53,0±7,6	,580	,695	50	51,0±8,4	50	54,7±5,5	**,012**	,419
DCS	retention	25	51,6±8,9	25	50,8±8,5	,746	,767	50	48,5±11,9	50	50,7±7,2	,266	,627
	learning	25	42,8±11,0	25	47,2±10,1	,147	,171	50	37,9±14,4	50	44,7±11,6	**,011**	,514
NVLT	learning	25	44,3±10,7	25	45,5±10,1	,676	,679	50	41,7±10,2	50	45,9±8,5	**,027**	,121

a: standardized T-values (mean±SD; corrected based on norms of the corresponding test manual). b: independent samples T-test; c: Multivariate Analysis of Variance including the averaged performance in tests of information-processing speed as a covariate.

IPS = Information-processing speed; AVLT = Auditory Verbal Learning Test; ROCF = Rey-Osterrieth-Complex-Figure; DCS = Diagnosticum For Cerebral Damage; VLT = Verbal Learning Test; NVLT = Nonverbal Learning Test; del. recall = delayed recall; RT = reaction time; Vis. RT = reaction time for visual stimuli; Aud. RT = reaction time for auditory stimuli.

Table 9. Correlations between memory, MRI, and IPS.

		IPS	NBV	Corti. thickn.	NHV left	NHV right	T1LV	T2LV
early MS (< 2 years of MS)								
VLT	learning	-,03	-,14	-,09	-,01	,00	-,27	-,23
late MS (> 12 years of MS)								
AVLT	del. recall	,51***	,10	,24	*,53****	,42**	-,01	-,05
VLT	learning	-,06	,09	*,27†*	,30*	,05	-,10	-,06
ROCF	del. recall	,40**	,11	,13	*,25†*	,29*	,06	,06
DCS	learning	,50***	,21	,38**	*,29†*	*,26†*	-,07	,01
NVLT	learning	,09	,14	,32*	*,29†*	-,02	-,20	-,10

Only those memory tests were evaluated that were found to be significantly lowered in patients compared to controls.
Correlations corrected for age and sex; †: p<.10; *: p<0.05; **: p<0.01; ***: p<0.001.
IPS = Information-processing speed; NBV = normalized brain volume; Corti. Thickn. = Cortical thickness; NHV = normalized hippocampal volume; T1LV = log-transformed T1 lesion volume; T2LV = log-transformed T2 lesion volume; AVLT = Auditory Verbal Learning Test; ROCF = Rey-Osterrieth-Complex-Figure; DCS = Diagnosticum For Cerebral Damage; VLT = Verbal Learning Test; NVLT = Nonverbal Learning Test.

MRI

The group means show that all parameters were significantly different between EMS and LMS (**Table 10**).

Table 10. Results of MRI in MS-patients with a short versus long disease duration.

	Early MS[a]	Late MS[b]	p[c]
N	25	50	
Median NBV, cm^3 [min-max]	1567 [1459-1721]	1452 [1154-1669]	**,000**
Median Cortical thickness, mm [min-max]	2,41 [1,88-2,57]	2,30 [1,85-2,54]	**,002**
Mean NHV left, cm^3 (SD)	2,66 (0,45)	2,39 (0,38)	**,006**
Mean NHV right, cm^3 (SD)	2,63 (0,43)	2,43 (0,41)	**,043**
Median T1LV, cm^3 [min-max]	1,39 [0,34-10,19]	4,54 [0,35-29,03]	**,000**
Median T2LV, cm^3 [min-max]	4,20 [0,73-19,49]	13,18 [2,27-57,37]	**,000**

a: disease duration < 2 years, b: disease duration > 12 years; c: Mann-Whitney Test or t-Test;
NBV = normalized brain volume; NHV = normalized hippocampal volume; T1LV = T1 lesion volume; T2LV = T2 lesion volume.

LMS

Left and right NHV were correlated with verbal memory tests, whereas cortical thickness was correlated with two tests for visual memory (**Table 9**). NBV (r = .33), NHV left (r = .37), NHV right (r = .30, all p < .05), and cortical thickness (r = .28, p < .10) were also correlated with IPS_z.

The regression analyses (**Figure 7**) revealed that IPS_z was the strongest predictor for performance in the AVLT, ROCF, and DCS, explaining between 17 % and 28 % of the variance. Sex and left NHV were significant predictors for performance in both verbal memory scores (i.e., VLT, AVLT), explaining between 7 % and 17 % variance. Cortical thickness was the only predictor for performance in the NVLT.

3.2.2 EMS

In EMS, correlations between memory, IPS and MRI were only evaluated for performance in the VLT and did not reveal any significance (**Table 9**, **Figure 7**).

Early MS (n=25)	**VLT - learning** n.s.					
Late MS (n=50)	**AVLT - delayed recall** F(3, 47) = 15.31, p<.001, adj. R^2=0.477		**VLT - learning** F(2, 47) = 5.59, p<.01, adj. R^2=0.164		**ROCF - delayed recall** F(1, 47) = 9.46, p<.01, adj. R^2=0.171	
		std. β / ΔR^2		std. β / ΔR^2		std. β
	IPS	0.400** / 0.26	**Sex**	-0.371** / 0.12	**IPS**	0.413**
	Sex	-0.454*** / 0.17	**NHV left**	0.290** / 0.08		
	NHV left	0.283* / 0.07				
	DCS - learning F(1, 47) = 18.81, p<.001, adj. R^2=0.275		**NVLT - learning** F(1, 47) = 4.97, p<.05, adj. R^2=0.078			
		std. β		std. β		
	IPS	0.539**	**Corti. thickn.**	0.312*		

Figure 7. Stepwise regression analyzes of impaired memory performance in patients with an early or a late disease stage.

Regression models included normalized brain volume (NBV), normalized hippocampus volume left (NHV left), normalized hippocampus volume right (NHV right), cortical thickness (Corti. Thickn.), as well as age, sex, depression, and fatigue as possible predictors. The minimum significance level for entry and for staying in the equation was 0.05 and p=.1 to exit. *IPS = Information-processing speed; AVLT = Auditory Verbal Learning Test; ROCF = Rey-Osterrieth-Complex-Figure; DCS = Diagnosticum For Cerebral Damage; VLT = Verbal Learning Test; NVLT = Nonverbal Learning Test.*

3.4. Discussion

Previous studies on MI in MS were conflicting in respect to possible early manifestations of MI and to the role hippocampal damage might play. Three methodological details that possibly contributed to these inconsistencies were accounted for in the present investigation of MI: disease stage, memory assessment, and slowed IPS. We found significant MI across different assessment paradigms in the LMS group, whereas the EMS group appeared to be cognitively preserved. Slowed IPS was found to be the most robust predictor for impairment in memory, followed by left-sided hippocampal atrophy for verbal and cortical thinning for visual memory.

Our findings both confirm and extend the results from previous studies that found MI as a prevalent symptom of MS. The rate of 43% MI in LMS corresponds well with prior data (Planche et al., 2015; Vanotti, Benedict, Acion, & Cáceres, 2009), although the effect sizes suggest a slightly lower severity of MI in our sample (Thornton & Raz, 1997). A distinctive feature of the present study was the use of several different test paradigms. We found elevated impairment rates in each test suggesting that MI in MS is detectable independently of learning material (verbal, visual), encoding (incidental, intentional), and retrieval (free recall, recognition, recurring recognition). This indicates a more global pattern of MI which corresponds with findings from two meta-analyses of MI in MS (Prakash et al., 2008; Thornton & Raz, 1997).

In contrast, we found no evidence for such a global effect on memory functioning in EMS, and also no support for the idea of a differential pattern of MI in EMS. Instead, our sample appeared to be unaffected by MI across several sensitive and validated memory test paradigms. This suggests that the type of memory assessment may not be the reason for conflicting findings of impaired (Grant et al., 1984; Potagas et al., 2008; Schulz et al., 2006; Sicotte et al., 2008) versus well preserved memory functions in EMS (Kern et al., 2015; Nygaard et al., 2015).

However, it has to be questioned whether the EMS sample was representative. On one hand, a selection bias in respect to cognitive functioning seems unlikely because the recruitment was performed consecutively at all sites and biased only by the search for

matching patients. On the other hand, a sample of 25 patients always carries the risk of being non-representative by chance in respect to relevant sample characteristics such as length of the infra-clinical course, age, sex, education, physical disability, depression and fatigue (Prakash et al., 2008). The present sample of EMS can be considered representative in respect to age (i.e., 29 years), sex (32% males), disease duration (1 year), and level of education (Krings, 2011), but not in respect to depression and fatigue (severe cases excluded; CES-D=13). Also, the length of the infra-clinical course remains unknown. Higher rates of MI have been found in samples of EMS that were characterized by older ages (e.g., 37-42 years (Amato, Portaccio, Goretti, Zipoli, Iudice, et al., 2010; Grant et al., 1984; Schulz et al., 2006; Sicotte et al., 2008)), elevated levels of depression (e.g., CES-D=33 (Glanz et al., 2007)), or higher rates of male patients (e.g., 46% males (Potagas et al., 2008)). It has to be noted though that the present study was not designed to draw conclusions on the MI prevalence in EMS. Thus, the results only suggest that the findings of well-preserved memory functions in small EMS samples (Brissart et al., 2013) may not be due to an incomprehensive memory assessment.

An important finding of the present study is the association between slowed IPS and MI in LMS. This correlation was evident in tests assessing visual and verbal memory using the same paradigm that all standard screening tests for MI in MS are based on (i.e., learning over trials) (Langdon et al., 2012). This corresponds well with investigations of working memory in MS that also revealed large contributions of IPS to impairment (Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011). A global factor of decreased cognitive processing efficiency has also been found in the validation study of the MACFIMS battery involving IPS, executive functions, working memory, and visual memory (Benedict, Cookfair, et al., 2006). Recently, Sacco et al. speculated about a global processing efficiency factor as well, after finding that nearly all of the patients in their study suffered from slowed IPS although they were strictly selected for MI (Sacco et al., 2015).

Another important finding of the present study is that IPS deficits were not only associated with MI but also with hippocampal atrophy. The same has been found using the SDMT (Debernard et al., 2015; Koenig et al., 2014) and the PASAT (Longoni et al., 2015) as a screening test for IPS deficits. In fact, it is a common finding that atrophy in different areas

(e.g., hippocampus, thalamus, caudate) are correlated with cognitive impairment simultaneously (Daams et al., 2015; Damjanovic et al., 2017; Pinter et al., 2015), possibly due to shared variance (Longoni et al., 2015). Therefore, the present correlation between hippocampal atrophy and IPS may be explained by the effect of unspecific tissue loss on cognitive functioning. According to recent models, diffuse cerebral damage could lead to cognitive inefficiency in MS by disconnecting broader cognitive networks (P. Calabrese & Penner, 2007; Dineen et al., 2009; Rocca et al., 2015; Schoonheim et al., 2015).

Thus, our study suggests that slowed IPS could be a mediator that needs to be accounted for in correlation analyses of MRI and MI. In the present study, such an analysis revealed that additionally to key contributions of IPS, structural MRI parameters remained as relevant predictors for MI in MS (Kiy et al., 2011; Planche et al., 2015; Sacco et al., 2015; Sicotte et al., 2008). However, a hippocampal contribution was only evident in verbal MI (Koenig et al., 2014; Pardini et al., 2014) and our data implies that one reason for this and similar findings (Anderson et al., 2010; Damjanovic et al., 2017; Sacco et al., 2015) might be a more dominant involvement of cortical damage in visual MI. This could explain why visual but not verbal memory deficits have been found to be associated with impairment in working memory, executive functions and IPS (Benedict, Cookfair, et al., 2006).

Several limitations have to be considered regarding this study. First and foremost, interpretation of the results in the EMS group is limited by its small sample size. The so achieved statistical power was not sufficient to reveal significance of smaller effects on MI. Thus, preclinical disturbances in the AVLT delayed recall, NVLT and DCS learning cannot be excluded. The sample size also precludes valid conclusions on the prevalence of MI in EMS and especially a comparison to the larger LMS group. A direct comparison of the correlations between EMS and LMS is also not feasible because of the differences in sample size and MI incidence. Secondly, the findings in LMS cannot be generalized onto groups that were not included in the present study, i.e. groups with intermediate disease durations (2 to 12 years), severe disability (median EDSS > 3.3), or PPMS. These groups may be characterized by a specific pattern of MI that is less confounded with IPS. Moreover, possible correlations to focal cortical thinning were not evaluated. Thirdly, the use of different MRI scanners in a multicentre study can be source of error. However, the standardization of image acquisition

and analysis in the present study was adequate to obtain reliable data (Damjanovic et al., 2017), and moreover, patients were distributed unsystematically across sites which minimizes systematic errors. Lastly, a possible mediating role of working memory impairment between IPS and memory deficits cannot be excluded because it was not assessed.

In conclusion, this study suggests that later stages of MS are characterized by unspecific memory deficits that relate to a generally decreased information-processing efficiency as well as to tissue loss in the left hippocampus and the cortex. Future studies should include IPS as a covariate for MI.

4. Study three: A smart peek: Visual processing parameters in early vs. late MS refer to cognitive ability.

4.1. Introduction

Cognitive impairment (CI) can affect patients with multiple sclerosis (MS) from the beginning and is regarded as an important predictor of disease course and functional outcome (Deloire, Ruet, Hamel, Bonnet, & Brochet, 2010; Langdon, 2011). Therefore, the identification of subjects at risk for cognitive decline is considered as a main task for current research (Rocca et al., 2015), and finding assessment instruments for early detection of cognitive impairment as an urgent requirement.

A large part of MS-related CI can be accounted for by a general processing efficiency factor, as it is reflected by measures of processing speed like the symbol digit modalities test (Costa et al., 2017). One influential perspective on general cognitive effectiveness, which is mainly invoked by intelligence research, posits that it has a close association with the capability to extract information from rapid visual displays (Deary, Der, & Ford, 2001; Luck & Vogel, 2013; Tachibana, Namba, & Noguchi, 2014). In the present paper, we adopt such a perspective based on a mathematically formalized theory, the “theory of visual attention” (TVA) (Bundesen, 1990). TVA can be used to separate visual processing capacity into four distinct components from performance in a simple psychophysical task (Foerster et al., 2016). This TVA-based assessment has been successfully applied to patients with different neurological disorders in over 30 clinical studies (Habekost, 2015) and was recently found to be sensitive to MS-related cognitive fatigue (Kluckow et al., 2016). We investigated its potential to detect abnormalities in MS, and to function as a possible index of CI.

TVA-based whole report was applied to 2 groups of MS-patients, one at a very early, one at a later disease stage. We asked which of the TVA-based components of visual processing capacity are already impaired at an early stage, and how the pattern differs from the late stage. Finally, we assessed how TVA-based parameters of visual processing capacity relate to

disease progression and the patients' cognitive status as measured by a neuropsychological test battery targeting key areas of CI.

4.2. Methods

The present paper reports results of a multi-center, cross-sectional study that was designed to compare visual processing capacity, cognitive functions and associated MRI markers in early and late MS. Since first signs of CI can occur very early in MS and later deterioration results from longer time periods (Amato et al., 2001), the study included patients with disease durations of either less than 2 years or more than 12 years. To control for possible confounders, patients were recruited as individual pairs matched for age at disease onset, sex, and education.

The study was approved by the local Ethical Committees. All participants provided written informed consent prior to participation.

Subjects

77 patients with a first clinical demyelinating event related to MS or a definite MS (Polman et al., 2005) were recruited from 5 MS-centers in Germany (Wermsdorf, Halle, Magdeburg, Rostock, Teupitz) between February and September 2011. Exclusion criteria were a relapse or corticosteroid treatment 4 weeks prior to neuropsychological assessment, visual acuity <0.2, severe fatigue (i.e., Weimus ≥ 52; (Flachenecker et al., 2006)) or depression (i.e., CES-D ≥ 39; (Hautzinger & Bailer, 1993)), alcohol abuse, pregnancy, and other relevant serious neurological and internal medical diseases as well as exclusion criteria for MRI. A sex ratio of 1 : 2-3 (m : f) was aimed at. Patients were assigned to 2 groups, one group having a disease duration of <2 years from the first clinical event (early MS, EMS, N = 25) and the other group a disease duration >12 years (late MS, LMS, N = 52). Patients were individually matched with respect to age at disease onset (±3 years), sex and education, i.e., two matching LMS-patients were recruited after inclusion of one EMS-patient. More LMS-patients were recruited to account for the higher variety of structural and cognitive changes at later disease stages.

The performance of MS-patients in the TVA-based whole report procedure (described below) was compared to that of control subjects taken from a panel of healthy subjects who have been assessed during the course of our TVA-based studies under standardized conditions. Based on these existing data, 2 control groups, i.e., cEMS and cLMS were formed separately for each patient group, matched for age, sex, and education.

TVA-based assessment of visual processing capacity

Visual processing capacity was assessed by using a simple psychophysical task, the whole report of brief letter arrays in combination with a TVA-based modeling of the individual test performance. This procedure has been employed in several previous studies and a detailed description can be found there (Bublak et al., 2011). The task lasted approximately 30 minutes and included a pre-test period comprising 24 trials, followed by 192 experimental trials (**Figure 8**). Four independent parameters were computed that constitute visual processing capacity: the minimum time where conscious visual processing starts (perceptual threshold, t_0); the number of visual objects that can be processed per second (processing rate, C); the number of visual objects that can be maintained in parallel within visual short-term memory (VSTM storage capacity, K); the additional time a visual percept is available for processing due to visual persistence (iconic memory buffering, μ). Congruent testing conditions and procedures were assured by intensive training of examiners before the project started.

Exposure durations were determined for each subject individually in a pre-test phase to adjust for differences in baseline performance between subjects. This way, the data gathered in the main test would allow optimal modeling of each subject's individual growth function of visual information uptake by excluding extreme exposure durations (i.e., durations below the threshold of conscious perception or durations beyond ceiling performance). For this purpose, the whole report was applied with masked displays and a fixed exposure duration. The criterion was an average of one correctly reported letter per trial (i.e. 20% report accuracy) in a series of 24 masked trials (12 for each hemi-field). The exposure duration determined during the pre-test was then used as the intermediate exposure duration in the experimental session, together with a shorter (half as long) and a longer (twice as long), exposure duration.

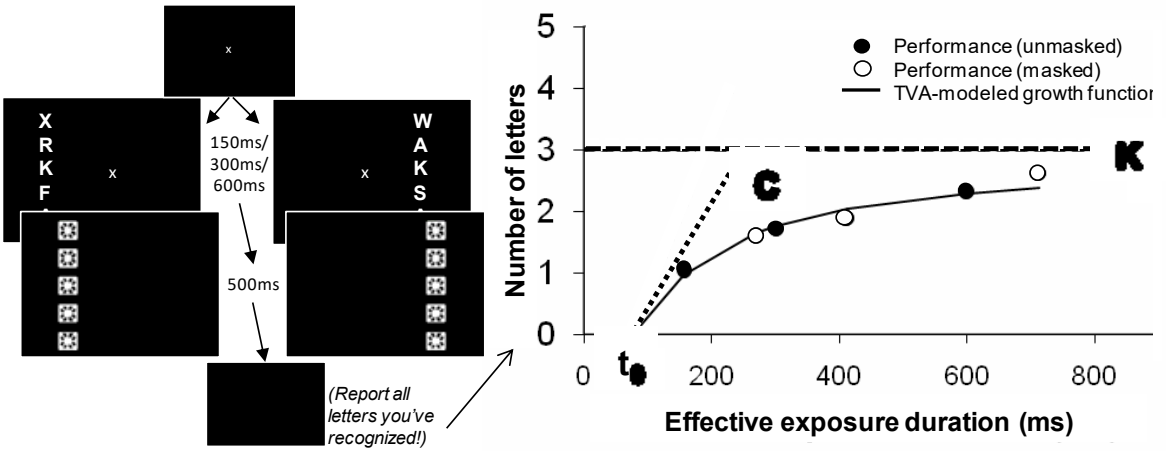

Figure 8. TVA-based assessment of visual processing capacity.

(Left): At each trial, five random letters appeared either on the left or right side of the fixation cross. The exposure duration of the letter array was chosen from 3 predetermined lengths (i.e., short, intermediate, long). Thereafter, either a blank screen or a screen containing masks for each letter was displayed. Side of presentation, exposure duration and masking were randomly chosen. Subjects were asked to verbally report all letters they had identified and could report them in any order and with no emphasis on speed of report. The experimenter recorded the reported letter(s) and initiated the next trial after the subject had indicated that he/she was ready. (Right): Performance was evaluated as the mean number of correctly reported letters at 6 different 'effective' exposure durations (i.e., 3 exposure durations * 2 masking conditions). This data was used to model an exponential growth function according to a maximum likelihood method. The resulting curve was characterized by the three parameters reflecting visual processing capacity: The slope at the curves' origin determines the processing rate C, the asymptote determines visual short-term-memory storage capacity (K); the origin determines the perceptual threshold (t_0). Additionally, the performance difference between unmasked and masked trials determines iconic memory buffering (μ).

Neuropsychological assessment

Conventional neuropsychological assessment was performed on a separate day, 2 weeks before or after the TVA-based assessment. A comprehensive test battery was administered in a single 1.5-hour session to assess different aspects of information-processing speed, verbal memory, visual memory, and visuo-constructive abilities (**Table 11**). Composite scores were computed by averaging the z-normalized results of the corresponding tests after correction for age, sex and education (based on normative data of the test manuals and results from an individually matched control group (Köhler et al., 2017). Additionally, results of the symbol digit modalities test (SDMT), a widely accepted standard instrument for assessing cognition in MS patients (Benedict et al., 2017; Van Schependom et al., 2014), were also obtained from 56 patients (20 EMS, 36 LMS) who agreed to a follow-up assessment (this follow-up assessment was performed 4.25 years (Min = 3.75, Max = 5.0, SD = 0.24) after the initial evaluation).

Table 11. Cognitive assessment battery.

Domain	Test[a]	Concept
Information-processing speed	Alertness	Response time to a simple visual stimulus appearing after an auditory cue or no cue
	Divided attention	Response time to auditory and visual stimuli presented in parallel
	Flexibility	Response time to complementary visual target stimuli in an alternating manner in a "set-shifting" task
	SDMT	Substitution task in which nine numbers have to be paired with abstract symbols as rapidly as possible according to a provided key
Visuo-constructive abilities	ROCF	Copying a complex figure graphically.
Verbal memory	AVLT	Learning a list of orally presented nouns with immediate and delayed retrieval
	VLT	Recurring recognition test of non-words
Visual memory	ROCF	Delayed free reproduction of a previously copied figure (memory component was unannounced)
	DCS	Learning nine different geometric figures and the order they are presented at over the course of three trials
	NVLT	Recurring recognition test of geometric and irregularly shaped figures

a: Tests were performed in the following fixed order: AVLT (learning), ROCF (copy), alertness, divided attention, flexibility, AVLT (recall, recognition), ROCF (recall), DCS, VLT, and NVLT. The SDMT was applied at a follow-up assessment 4.25 years after the original evaluation for comparison with the literature.
SDMT = Symbol Digit Modalities Test; ROCF = Rey-Osterrieth Complex Figure Test; AVLT = Rey Auditory Verbal Learning Test; VLT = Verbal Learning Test; DCS = Diagnosticum fuer Cerebralschaedigung; NVLT = Nonverbal Learning Test.

Statistical analyses

Statistical analyses were performed with SPSS and applied to complete datasets only.

Group differences of the TVA-based parameters were evaluated by using independent samples t-test after verifying normal distribution (one-sample Kolmogorov-Smirnov Test).

Associations to clinical and demographic variables were evaluated by using Spearman's rank correlation (age, EDSS, disease duration, depressive mood, fatigue) or independent samples t-test (sex, education, history of optic neuritis). Correlations between TVA parameters and conventional neuropsychological performance were analyzed by using Pearson correlation. The relative contribution of TVA-based parameters to the neuropsychological outcomes was

analyzed by using stepwise regression analyses including clinical and demographic variables as predictor variables in block 1 and the TVA-based parameters in block 2.

4.3. Results

69 patients were included into the present analysis (**Table 12**). One patient withdrew his consent to participate, two patients had insufficient visual acuity to perform the TVA test, and five patients were excluded from the analysis because their TVA data was not recorded due to a software error.

Table 12. Clinical and demographic variables.

	early stage[a]		late stage[b]	
	EMS	cEMS	LMS	cLMS
N	24	24	45	45
Sex (male : female)	1 : 2.43	1 : 2.43	1 : 2.46	1 : 2.75
Age (years)	28.9 (6.7) [20-47]	29.0 (7.1) [20-48]	**45.1 (7.9) [32-61]*** **	44.7 (8.5) [27-60]
Education ≥12 years (N (%))	9 (38%)	11 (46%)	11 (24%)	19 (42%)
Age at disease onset (years)	28.0 (7.0) [18-47]		28.2 (6.8) [19-46]	
Disease duration (years)	1.0 (0.8) [0-2]		16.9 (5.4) [10-37]	
EDSS (Median [min-max])	1.8 [0-6]		**3.0 [0-8]****	
History of optic neuritis (N (%))	11 (46%)		19 (42%)	
Depression (CES-D)	13.0 (9.9) [1-36]		13.1 (9.0) [0-34]	
Fatigue (Weimus)	19.9 (16.6) [0-50]		26.6 (14.6) [0-51]	

Values are displayed as mean (SD) [min-max]. Group differences were tested by using Fisher's Exact Test (sex, education) or independent samples t-test (*: p<.05; **: p<.01; ***: p<.001).
a: patients with a disease duration of < 2 years and matched controls.
b: patients with a disease duration of > 12 years and matched controls.
EMS = early MS; LMS = late MS; cEMS = with EMS matched control group; cLMS = with LMS matched control group; EDSS = Expanded Disability Status Scale; CES-D = Center for Epidemiologic Studies Depression Scale; g: Weimus = Wuerzburger Erschoepfungsinventar bei MS.

Visual processing capacity

Processing rate C, visual short term memory capacity K, and iconic memory µ were significantly lowered in both MS groups compared to controls (**Table 13**). In contrast, the perceptual threshold t_0 was only elevated in LMS, not in EMS.

A direct contrast of EMS and LMS revealed that the effects on parameters C and μ were more pronounced in LMS (both $p < .05$), whereas no additional effect was found with respect to K ($p = .647$).

Table 13. TVA-based visual processing capacity in early and late stages of MS.

	MS	control	p
early stage MS			
Perceptual threshold t_0 (msec)	11.8 (12.8)	9.09 (16.3)	.518
Processing rate C (elements/sec)	20.66 (5.7)	26.12 (11.6)	**.045**
VSTM capacity K (number of elements)	2.59 (0.50)	3.41 (0.70)	**.000**
Iconic memory μ (msec)	102 (40.3)	142 (48.6)	**.003**
late stage MS			
Perceptual threshold t_0 (msec)	46.8 (39.3)	24.8 (30.9)	**.004**
Processing rate C (elements/sec)	17.15 (5.9)	20.55 (8.1)	**.025**
VSTM capacity K (number of elements)	2.53 (0.51)	3.15 (0.61)	**.000**
Iconic memory μ (msec)	79 (45.3)	151 (58.0)	**.000**

Results are displayed as mean (SD). Group differences were tested by using independent samples t-test.
TVA = Theory of visual attention; VSTM = visual short term memory.

Associations with clinical and demographic variables

The analyses revealed age as the only demographic variable that was significantly associated with visual processing capacity in both groups, affecting primarily perceptual threshold t_0 and to a lesser extent processing rate C (**Table 14**). In LMS, education was associated with t_0 as well. Sex, however, was not associated with any of the visual processing parameters in either group.

With respect to the clinical variables, no associations with optic neuritis and disease duration were evident in either group (**Table 14**). However, in LMS a series of significant weak to moderate correlations between the perceptual threshold t_0 and several clinical variables was apparent including EDSS, depressiveness, and fatigue (**Table 14**). This pattern was not evident in EMS and not resembled by the other three visual processing components (i.e., C, K, and μ).

Table 14. Associations between TVA-based visual processing capacity and clinical and demographic variables.

	t_0	C	K	μ
Early stage MS				
Age	**.460***	-.219	-.024	.168
Sex (female vs. male)	13.6 (13) vs. 7.6 (13)	20.9 (6) vs. 20.0 (6)	2.5 (0.6) vs. 2.8 (0.2)	106 (39) vs. 92 (45)
Education (≥12y vs. <12y)	10.7 (9) vs. 12.6 (15)	21.3 (6) vs. 20.2 (6)	2.4 (0.6) vs. 2.7 (0.4)	112 (37) vs. 97 (42)
EDSS	-.037	.107	.013	-.018
Disease duration (years)	-.319	-.061	.181	.234
Optic neuritis[a] (yes vs. no)	13.5 (15) vs. 10.5 (11)	18.7 (4) vs. 22.3 (7)	2.7 (0.4) vs. 2.5 (0.6)	112 (50) vs. 94 (29)
Depression (CES-D)	.043	.150	.122	-.057
Fatigue (Weimus)	.148	.037	**.424***	.053
Late stage MS				
Age	**.357***	**-.333***	.118	-.138
Sex (female vs. male)	42.0 (37) vs. 58.4 (43)	16.7 (6) vs. 18.2 (6)	2.5 (0.5) vs. 2.5 (0.4)	83 (47) vs. 70 (40)
Education (≥12y vs. <12y)	**22.8 (28) vs. 54.5 (39)***	18.1 (5) vs. 16.9 (6)	2.6 (0.5) vs. 2.5 (0.5)	94 (40) vs. 74 (47)
EDSS	**.454****	-.200	.216	-.169
Disease duration (years)	.075	-.096	.162	-.051
Optic neuritis[a] (yes vs. no)	47.5 (39) vs. 46.3 (40)	16.7 (6) vs. 17.5 (6)	2.6 (0.6) vs. 2.5 (0.5)	84 (47) vs. 76 (44)
Depression (CES-D)	**.298***	-.193	.142	.090
Fatigue (Weimus)	**.328***	-.151	.151	.084

Associations with continuous variables were tested by using Spearman's rank correlation, those with dichotomous variables by comparing group means (SD) using independent-samples t-test (†: p<.10; *: p<.05; **: p<.01).

a: Presence of optic neuritis in the patients' clinical history.

t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory; EDSS = Expanded Disability Status Scale; CES-D = Center for Epidemiologic Studies Depression Scale; Weimus = Wuerzburger Erschoepfungsinventar bei MS.

Association with neuropsychological assessment

In the EMS group, cognitive functioning, as assessed by conventional neuropsychological tests, appeared to be widely preserved (**Table 15**). The largest deviations from the normative data were present in verbal and visual memory; however these did not reach statistical significance in this sample of 24 patients. Weak correlations between t_0 and verbal memory, as well as between t_0 and visual memory were found (**Table 15**). Another weak, but

statistically not significant (p = .13) correlation was indicated between the TVA-based processing rate C and measure of information-processing speed.

In the LMS group, information-processing speed, verbal and visual memory were affected by MS (**Table 15**). A striking pattern of mostly moderate correlations between the perceptual threshold t_0 and neuropsychological performance was evident across all evaluated cognitive domains (**Table 15**). As in the EMS group, C and information-processing speed were found to be weakly correlated as well.

Table 15. Cognitive functioning in early and late MS and its correlation to visual processing capacity.

	Cognitive functioning [a]	Correlation to visual processing [b]			
	mean z (SD)	t_0	C	K	μ
Early stage MS					
Information-processing speed	0.13 (0.6)	-.167	.318	.101	-.048
Visuo-constructive abilities	-0.02 (1.1)	-.153	.133	-.011	.206
Verbal memory	-0.11 (0.7)	**-.461***	.122	.007	.244
Visual memory	-0.10 (0.7)	*-.356†*	.007	.156	.250
Late stage MS					
Information-processing speed	**-0.59 (0.9)*****	**-.504****	**.310***	.134	.108
Visuo-constructive abilities	0.00 (1.2)	**-.661****	.113	.059	*.231*
Verbal memory	**-0.48 (0.9)***	**-.359***	.053	-.181	-.066
Visual memory	**-0.46 (1.0)***	**-.534****	*.227*	-.003	.095

a: Composite scores were computed by averaging the z-normalized results of the corresponding cognitive tests after correction for age, sex and education. Group effects between patients and individually matched controls were assessed by using the t-test.
b: Pearson correlation coefficients.
†: p<.10; *: p < .05 **: p < .01.
t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory.

The regression analyses confirmed that in LMS, t_0 was an independent predictor of information-processing speed, visual memory, and visuo-constructive abilities even after controlling for all clinical and demographic variables (**Figure 9**). In EMS, t_0 remained to be a significant predictor (std. β = -0.580, p < .01) of verbal memory (F(2, 23) = 10.90, p<.001, adj. R^2 = 0.463) additionally to sex (std. β = -0.56, p < .01).

INFORMATION-PROCESSING SPEED F(2, 43) = 9.59, p<.001, adj. R^2=0.285			**VISUAL-SPATIAL CONSTRUCTIONAL ABILITY** F(2, 43) = 15.88, p<.001, adj. R^2=0.409		
	std. β	ΔR^2		std. β	ΔR^2
EDSS	-0.292†	0.22	**EDSS**	0.004	0.10
t_0	-0.361*	0.10	**t_0**	-0.663***	0.34
VERBAL MEMORY F(2, 43) = 5.66, p<.01, adj. R^2=0.178			**VISUAL MEMORY** F(2, 43) = 8.89, p<.001, adj. R^2=0.268		
	std. β	ΔR^2		std. β	ΔR^2
Sex	-0.303*	0.13	**Fatigue**	-0.139	0.10
EDSS	-0.297*	0.09	**t_0**	-0.485***	0.21

Figure 9. Stepwise regression analyses of cognitive performance in late stage MS.

Regression models included age, sex, education, disease duration, EDSS, history of optic neuritis, depressiveness and fatigue in block 1 and the TVA-based parameters constituting visual processing capacity, i.e., perceptual threshold (t0), processing rate (C), visual short-term memory capacity (K), and iconic memory (μ) in block 2. The minimum significance level for entry and for staying in the equation was 0.05 and p=.1 to exit.

The detailed analysis of information-processing speed in LMS showed that after correction for EDSS and age, respectively, t_0 remained to be correlated with reaction time for visual and auditory stimuli in the test of divided attention, as well as to qualitative measures in the tests of divided attention and flexibility. C remained to be correlated with reaction time in the flexibility test after correction for age (**Table 16**).

Table 16. Pearson correlations [corrected partial correlations] between different aspects of information-processing speed and visual processing capacity in late stage MS.

		TVA-based parameters			
		t_0	C	K	μ
Alertness	reaction time	-.201† [.059]	**.303*** [.237†]	-.157	-.077
Divided attention	reaction time visual	**-.393** [-.297*]**	.218† [.208†]	*.232†*	*.222†*
	reaction time auditory	**-.387** [-.278*]**	.078 [.067]	**.312***	.130
	errors	**-.355**** [-.247†]	**.280*** [.231†]	-.161	-.052
	omissions	**-.296* [-.291*]**	.106 [.091]	.130	.180
Flexibility	reaction time	**-.369**** [-.245†]	**.285* [.262*]**	.134	.047
	errors	**-.359**** [-.211†]	.194 [.111]	.082	.039
SDMT (N=36)	correct answers	**-.608** [-.466**]**	**.312*** [.252†]	.177	.205

Values represent correlation coefficients. Partial correlation reflect corrections for those clinical and demographic variables that were significantly correlated with TVA-based parameters (t0: controlled for age and EDSS; C: controlled for age). Correlations were tested one-sided (†: p<.10; *: p < .05 **: p < .01.).

t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory.

4.4. Discussion

The TVA-based parametric assessment of visual processing capacity, comprising four distinct components, revealed evidence of widespread changes in patients with MS, both at an early and at a later disease stage. There was a differential pattern of impairment at the two different disease stages assessed. Even at an early stage (EMS), where CI as assessed by conventional neuropsychological testing was the exception, patients showed significant modifications in 3 of the 4 TVA parameters: i.e. iconic memory, VSTM storage capacity, and processing rate. The later stage (LMS) was characterized by a quantitative increase of parameter deviations, as well as by a qualitative change, i.e. the emergence of an elevated perceptual threshold. The threshold values had a significant relationship to disease progression in general and to impaired information-processing speed and visual memory functioning in particular.

The results of the present study are in line with the evidence that visual dysfunction is one of the most common clinical manifestations of multiple sclerosis (Sakai, Feller, Galetta, Galetta, & Balcer, 2011), and CI in MS is particularly prevalent in tasks involving visual processing (Kavcic & Scheid, 2011; Laatu, Revonsuo, Hämäläinen, Ojanen, & Ruutiainen, 2001; Lopes Costa et al., 2016; Moster, Wilson, Galetta, & Balcer, 2014; Utz et al., 2013). Accordingly, performance in our TVA-based whole report task could, in principle, be affected by damage at each level of the visual hierarchy, from the retina to higher order brain areas involved in attention functions. We would, however, suggest that elementary sensory deficits have a minor role, only, in accounting for our results, for the following reasons: Firstly, individual adjustment of exposure durations compensated for differences in sensory functions. Secondly, patients with and without a history of optic neuritis did not differ significantly with respect to any of the TVA-based parameter estimates. Nevertheless, as we did not include a direct measure of basic visual functions, like e.g. low-contrast letter acuity, an influence of basic sensory differences on our results cannot be completely ruled out. Note, however, that impairment of visual contrast sensitivity may, on the other hand, actually be an effective marker of post-geniculate white matter pathology in MS (Wu et al., 2007).

Recently, Fielding et al. (2015) have suggested that using behavioral tasks assessing oculomotor functions can tell a lot about the integrity of brain networks that form the scaffolding of cognition. In a similar vein, we would suggest that TVA-based assessment may also represent a sensitive index for the disruption of the brain networks underlying cognition. The visual perception and attention system is intimately connected with nodes of higher order brain networks underlying cognitive functions, with a large part of the cerebral cortex being responsive to visual input (Felleman & Van Essen, 1991). Therefore, measuring the efficiency of visual information uptake may provide a means for sensitively detecting network derangements. The possibility to validly map the integrity of neuro-cognitive networks may also be the reason why extracting information from rapid visual displays has long been known to be a good predictor of intellectual ability (see Deary et al., 2001).

According to this view, there would be no causal relationship between the parameters of visual information uptake, as provided by TVA, and cognitive functions. Instead, much like measuring body temperature as a global index of the activity of an infectious disease, assessing visual processing capacity may provide important information about different aspects of cerebral network functionality. For example, in a TVA-based study in normal subjects, individual differences in parameters K and C were found to be directly linked to structural differences within the long-association fronto-parietal white matter pathways (Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015). Similarly, in an earlier TVA-based study in patients with mild cognitive impairment and early Alzheimer's disease (AD) (Bublak et al., 2011), declines of VSTM storage capacity and processing rate as revealed at the stage of manifest dementia, were interpreted as indicating a disturbance of white matter connectivity appearing at later AD stages. On the other hand, an elevation of the perceptual threshold observed at the MCI stage, already, was suggested to reflect primary cortical pathology at this early stage of AD.

The results of the present study are complementary, with processing rate and VSTM storage capacity changed already in early MS patients, while perceptual threshold being increased in the group of subjects with late MS, only. Applying a similar rationale as described above in the case of AD, this result could mean primary affliction of white matter connectivity by MS-related brain pathology at an early stage, but additional cortical involvement at later stages.

However, such conclusions are clearly speculative and would need to be confirmed by MRI data using measures of lesion load and brain atrophy in combination with TVA-based assessment.

The TVA-based method appears to be well-suited for that purpose. Within the tri-factor model of processing speed introduced by Costa et al. (2017), TVA models one specific aspect, i.e. sensory speed within the visual modality, and it does so with reference to an explicit theoretical and mathematically formalized framework. It deconstructs sensory speed into distinct components reflecting both velocity and maintenance aspects of visual processing capacity. Moreover, these components appear to be differentially affected at different disease stages, which allows to generate testable hypotheses about the nature and the underlying pathology of different parameter patterns.

In summary, two important conclusions may be drawn from the present study. First, TVA-based assessment may be able to identify a reduction of processing efficiency even at an early disease stage, when conventional neuropsychological testing is still “silent”. Second, at a later stage, a single procedure may be able to provide a valid status description about cognitive functioning in general. Therefore, TVA-based assessment may bear great potential for cognitive assessment in MS-patients, in particular, for early identification of patients with an increased risk for cognitive decline. This may enhance the chance for early intervention, for which recent studies have already revealed promising approaches (Huiskamp, Dobryakova, Wylie, DeLuca, & Chiaravalloti, 2016).

Future directions for TVA-based investigations in MS patients may aim at underpinning parameter changes with MS-related brain pathology as derived from structural imaging data, controlling for the influence of clinical variables in a more representative patient sample, and collecting longitudinal data to prove the potential of TVA-based assessment as a valid tool for detecting imminent cognitive decline prior to its manifestation in conventional neuropsychological testing.

5. General Discussion

The aim of this thesis was to evaluate established and novel neuropsychological assessment strategies for cognitive impairment in MS. For this purpose, two carefully matched groups of patients were recruited, one at a very early disease stage and one at a late stage. Key domains of MS-related cognitive impairment were assessed by using traditional neuropsychological tests with a particular focus on memory functioning. Additionally, a novel, parametric approach for modeling visual information uptake based on a theory of visual attention (TVA) was used to assess four distinct components of visual processing capacity. In three studies, the acquired data was used to evaluate (1) the comparability of common classification criteria of cognitive impairment, (2) associations between memory performance, information-processing speed and structural MRI, and (3) the extent of TVA-based visual processing capacity decline in early versus late MS and its association with cognitive impairment and other disease-related variables.

For the first study, which focused on the definition of cognitive impairment, a systematic review of 179 original studies was conducted to provide an overview of the different criteria that are used to classify impairment and to evaluate whether criterion selection might be influenced by disease duration and other sample characteristics. Additionally, 75 healthy control subjects, individually matched to the MS patients, were recruited and analogously cognitively assessed to provide an adequate reference for false positive classification in the original data. Cognitive data of patients and controls was then used to evaluate the classification resulting from the most commonly used criteria.

The main implication from the first study was that classification criteria need to be better homogenized in respect to classification stringency. It was shown that a range of criteria are in use which can result in very different rates of cognitive impairment if the probability for false-positives is not matched. In turn, the study also demonstrated that if this probability is matched, it is of less relevance which exact neuropsychological tests are utilized and whether the classification is based on regression-based or manual-based norms, on impairment in specific domains or a composite score, or on a 1, 1.5, or 2 SD cut-off. However, the study clearly revealed that criteria selection has in fact been biased, i.e., liberal

criteria were more often applied in studies that evaluated patients with shorter disease durations. Moreover, it was suggested by the original data that in early MS only subtle signs of cognitive dysfunction become evident when compared to an adequate control group and it was therefore concluded that the significance of cognitive impairment in early MS might have been overestimated compared to later MS stages. It was therefore recommended that a more homogenized use of impairment classification should include a differentiation into mild, moderate and severe forms.

In the second study, MRI was applied to patients in both groups in order to derive estimates of MS-related neurodegeneration in a memory-specific region, i.e., the hippocampus, and in the white and grey matter. This data was used in a thorough neuropsychological evaluation of memory impairment in MS. The focus of this study was on methodological aspects that were not accounted for in previous studies of memory functioning in MS and that might explain past inconsistencies in respect to the presence of early memory impairment and correlations to hippocampal atrophy. For that reason, memory assessment went beyond standard word list and visuospatial learning and comprised three additional validated tests that were not a part of standard assessment batteries for MS (see chapter 1.2.3). Also, a potential mediating role of the most significant cognitive deficit in MS, i.e., slowed information-processing speed was accounted for and finally, effects of early and late MS on memory functioning were evaluated separately.

The study confirmed that there are subgroups of early MS patients that show no signs of meaningful memory impairment, even if they are comprehensively assessed. From these findings it was concluded that assessment differences may not be the reason for the discrepancy between studies that found early memory impairment and those that did not. It was speculated that subgroups can be well-preserved because of particular sample characteristics including younger age, shorter infraclinical course, higher proportion of females, advanced education, absence of depression and fatigue. The study also supported the notion that memory deficits in later stages are characterized by a rather global pattern and that this can be detected by different neuropsychological tests of episodic memory. The most important result of this study, however, was on the role of information-processing speed deficits. It was suggested by the presented data that on one hand, slowed

information-processing impacts memory performance in MS, and, on the other hand, is associated with atrophy across several memory-specific and unspecific brain regions. Thus, a considerable part of memory deficits in MS could be related to mental slowing that arises from accumulated tissue loss in later disease stages. Based on the latter findings, it was concluded that information-processing speed should be accounted for in future studies of MI in MS as a potential mediator or covariate.

The objective of the third study was to evaluate a novel, neuropsychological assessment strategy based on a theory of visual attention (TVA) at early and late MS stages. The innovative quality of TVA-based testing is that cognitive functions are not directly assessed by test performance itself as in traditional neuropsychological tests. Instead, performance is used to model visual attention as a mathematical function according to the equations provided by TVA. Characteristics of the resulting curve (such as its origin, slope, and asymptote) are then derived to quantify distinct components that constitute the capacity of selective visual attention. TVA-based testing is cognitively specific, reliable and sensitive to minor deficits. In the present study, an experimental software solution for TVA-based testing was introduced to clinical neuropsychologists at five German MS centers for the assessment of 75 patients and the obtained parameter estimates of visual processing were compared to reference values of healthy adults, indicators of MS-related disease progression and cognitive functioning.

A first conclusion from this study was that early visual processing deficits can be detected by using TVA-based testing at stages with well-preserved cognitive functioning. A second conclusion was that in later disease stages a different TVA-based deficit pattern emerges that is characterized by additional elevations of the perceptual threshold. A third conclusion was that the elevation of the perceptual threshold is indicative of cognitive impairment and disease progression. Although the study was not designed to elucidate whether the early deficits reflect cerebral pathology or sensorimotor damage, the existing literature of clinical TVA-based studies was reinterpreted in support of the former. More specifically, it was speculated that early visual processing deficits can be attributed to early white matter pathology and the later qualitative changes to additional cortical pathology. In future imaging studies TVA-based assessment might be applied to better understand the

underlying mechanism of cognitive impairment in MS. It was additionally discussed how an elevated perceptual threshold could explain previous findings of visual processing deficits in MS to support the notion of this parameter being a key determinant of visual processing deficits in later disease stages. Considering the fact that this was the first study to systematically assess TVA-based visual processing capacity at different disease stages, it was speculated that at early stages, TVA-based testing could have prognostic value for disease progression and cognitive decline; and at later stages, provide a marker of cognitive functioning in general. The study also showed that TVA-based testing is practicable for the evaluation of patients with varying levels of physical disabilities.

The most important limitation of all three studies was the sample size of the early MS group. On one hand, this limits the degree to which the results can be generalized; on the other hand, it makes it difficult to directly compare the results with the double the size late MS group. It is likely that in a larger, heterogeneous sample of early stage patients, cognitive impairment becomes more prevalent (Ruano et al., 2017). In contrast, the present sample of early MS included mostly well-preserved patients. Therefore, it would be very informative to replicate the present investigation in a larger group of patients with early MS and probable cognitive impairment.

The absence of a measured ecological validity is another limitation of the present evaluation. While cognitive impairment associated with stroke, Alzheimer's disease, or traumatic brain injury oftentimes has high face validity in respect to day-to-day living activities, this is not the case for mild cognitive impairment associated with MS. Also, MS patients' subjective complaints on cognitive functioning seem to reflect depression, anxiety, fatigue, and physical disability rather than objective indicators of cognitive impairment (Benedict et al., 2003; Hulst et al., 2014; Middleton, Denney, Lynch, & Parmenter, 2006). Thus, the clinical meaningfulness of different levels of cognitive impairment remains unclear. With respect to TVA-based assessment, Kluckow et al. (2016) have recently revealed an association between a decreased processing rate and objective fatigue. However, other promising approaches to link statistical significance in cognitive tests to meaningful levels of functional impairment have been introduced (Benedict et al., 2016) and therefore, future evaluations of

neuropsychological assessment strategies should include such measures of clinical meaningfulness.

One more important aspect that was not accounted for in this thesis is a longitudinal neuropsychological evaluation (Walker et al., 2011). First, patients evaluated in the present thesis might have been tested prior to study inclusion, especially the four who were under natalizumab treatment (DGNLL, 2014; Kunkel et al., 2015; Prosperini et al., 2016), which could have improved their performance due to practice effects (Jønsson et al., 2006). Second, it is an important task to identify reliable and valid neuropsychological tests for multiple testing and monitoring of disease progression and cognitive deterioration (Hoffmann et al., 2007). For example, cognitive monitoring is explicitly recommended for the duration of natalizumab treatment to alert clinicians of a possible Progressive Multifocal Leukoencephalopathy, a serious adverse event with a 24 % mortality rate (DGNLL, 2014). Therefore, it is an objective for future studies to evaluate the stability and sensitivity to the change of traditional and TVA-based assessment in different groups of MS patients. First insights might be provided by a longitudinal study that was conducted by our research group and that included the same groups evaluated as part of this thesis.

In conclusion, the present findings demonstrated that classification of cognitive impairment in MS is not fully comparable across different published criteria and needs to be better homogenized in respect to classification stringency. The findings also suggest that deficits in the speed of information processing have to be accounted for when evaluating memory functioning in MS patients because speed deficits affect memory. Finally, it was confirmed that a novel, TVA-based assessment strategy can be used to detect visual processing capacity decline at a stage when traditional cognitive assessment is still “silent” and in later stages may provide a valid estimate of cognitive functioning and disease progression.

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Abbreviations

μ	Iconic memory
AD	Alzheimer's disease
ANOVA	analysis of variance
AVLT	Auditory Verbal Learning Test
BVMT-R	Brief Visuospatial Memory Test – Revised
C	processing rate
cEMS	control group matched with EMS patients
CES-D	Center for Epidemiologic Studies Depression Scale
CI	cognitive impairment
CIS	clinically isolated syndrome
cLMS	control group matched with LMS patients
CNS	central nervous system
CVLT	California Verbal Learning Test
DCS	Diagnosticum For Cerebral Damage
EDSS	Expanded Disability Status Scale
EMS	early MS
IPS	information-processing speed
K	visual short-term memory storage capacity
LMS	late MS
MCI	mild cognitive impairment
MI	memory impairment
MRI	magnetic resonance imaging
NBV	normalized whole brain volume
NHV	normalized hippocampus volume
NVLT	Nonverbal Learning Test
OCT	optical coherence tomography
PASAT	Paced Auditory Serial Addition Test
PPMS	primary progressive multiple sclerosis
ROCF	Rey-Osterrieth-Complex-Figure-Test
RRMS	relapsing remitting multiple sclerosis
RT	reaction time
SDMT	Symbol Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
SRT	Selective Reminding Test
t_0	perceptual threshold
T1LV	T1 lesion volume
T2LV	T2 lesion volume
TAP	computerized Test Battery of Attention
TVA	Theory of visual attention
VLT	Verbal Learning Test
VSTM	visual short-term memory
Weimus	Wuerzburger Erschoepfungsinventar bei MS

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Supplement A: Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Table e1. Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Publication	Strategy[1]	Number of relevant parameters[2]	Critical number of abnormal Parameters	SD Cut-off	Stringency[3]	Criteria specifics	Test battery[4]	N	Disease Course[5]	Age		Disease duration		% CI[6]
										mean	SD	mean	SD	
(Achiron & Barak, 2003)	1	6	1	1.00	liberal		BRB-N + CDT	67	CIS, MS	32.3	10.3	0.1	0.1	94.00
(Achiron et al., 2013)	2	65	N/A	(1.00)	N/A	Composite score (average of normalized parameters) < -1 SD	GAB	1500	MS	40.5	SE: 0.3	9.7	SE: 0.2	27.68
(Amato et al., 2012)	1	10	2	1.68	fair		BRB-N + Stroop	55	RR, RIS	35.8	8.5	8.7	7.1	30.9
(Amato et al., 2004)	1	7	1	2.00	cons.		BRB-N	41	RR	35.1	8.6	4.0	2.8	56.10
(Amato et al., 2001)	1	12	3	1.68	cons.		nonstandard	45	RR, SP, PP	39.1	8.3	11.3	2.3	56.00
(Amato et al., 2006)	1	10	3	1.68	cons.		BRB-N + Stroop	163	bMS	44.5	7.7	20.8	5.3	49.00
(Amato, Portaccio, Goretti, Zipoli, Iudice, et al., 2010)	1	10	2	1.50	fair		BRB-N + Stroop	49	RR	36.9	8.9	2.9	1.7	31.00
(Batista et al., 2012)	3	10	(2)	1.5; 2	N/A	1) mean z score <-1.5 across 6 parameters of SDMT, PASAT, BVMT, and CVLT; or 2) 1 parameter >2SD and 2 parameters >1.5SD, or 2 Parameter >2SD across all 10 cognitive measures.	MACFIMS	58	MS	43.5	6.5	9.6	6.6	48.20
(Baumstarck-Barrau et al., 2011)	1	8	3	2.00	cons.		BRB-N	124	CIS, RR, SP, PP	45.1	10.8	Median: 9.9	Range: 0-31	37.00
(Benedict, Bruce, et al., 2006)	1	6	(2)	1.5; 2	N/A	1) 1 parameter ≥2SD and another ≥1.5 SD; or 2) 3 parameters ≥1.5 SD	nonstandard	82	RR, SP	44.6	8.5	12.2	8.2	59.80
(Benedict, Cookfair, et al., 2006)	1	11	2	1.50	fair		MACFIMS	291	RR, SP, PR, PP	45.4	8.9	N/A	N/A	59.50
(Benedict et al., 2004)	3	10	(2)	1.5; 2	N/A	1) mean z score <-1.5 across 6 parameters of SDMT, PASAT, BVMT, and CVLT; or 2) 1 parameter >2SD and 2 parameters >1.5SD, or 2 Parameter >2SD across all 10 cognitive measures.	MACFIMS + WCST	85	MS	42.4	9.3	N/A	N/A	35.00
(Benedict et al., 2003)	2	6	N/A	(1.50)	N/A	Composite score (average of normalized parameters) < -1.5 SD	nonstandard	50	RR, SP	42.6	7.2	10.1	6.6	24.00
(Bester et al., 2013)	1	6	2	1.60	cons.		nonstandard	26	bMS	53.4	7.1	25.8	9.6	38.00

Table e1. Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Publication	Strategy[1]	Number of	Critical	SD	Stringency[3]	Criteria specifics	Test battery[4]	N	Disease	Age		Disease duration		% CI[6]
(Borghi et al., 2013)	1	9	2	1.50	cons.		BRB-N	303	RR, PP, SP, RP	43.1	10.8	10.9	7.3	35.60
(M. Calabrese et al., 2009)	1	8	1	2.00	cons.		BRB-N	70	RR	34.8	Range: 18-55	8.4	Range: 1-18	34.30
(M. Calabrese et al., 2010)	1	7	1	2.00	cons.		BRB-N	100	RR	32.2	7.2	6.2	2.6	39.00
(Camp et al., 2005)	1	9	3	2.00	cons.		BRB-N	99	PP	48.6	9.7	10.4	7.0	21.21
(Camp et al., 1999)	1	11	3	2.00	cons.		BRB-N + VESPAR	63	PP, TP	47.7	9.9	11.6	7.1	28.60
(Correale et al., 2012)	1	6	3	2.00	cons.		nonstandard	43	bMS	37.2	7.1	10.8	0.6	47.00
(Deloire et al., 2005)	1	15	(2)	1.68	N/A	2 out of 10 tests abnormal (i.e. min. 1 parameter of each test abnormal)	BRB-N + nonstandard	58	RR	37.3	9.2	2.0	2.2	44.80
(Deloire et al., 2010)	1	12	2	1.68	fair		BRB-N + nonstandard	46	RR	38.6	8.7	2.0	2.3	47.80
(Deloire et al., 2006)	1	15	(2)	1.68	N/A	2 out of 10 tests abnormal (i.e. min. 1 parameter of each test abnormal)	BRB-N + nonstandard	57	RR	37.2	9.2	2.1	2.2	59.70
(Denney et al., 2008)	2	12	N/A	(0.5; 1)	N/A	Composite score (average of normalized parameters) < 0.5 SD and 1 out of 3 cognitive factor scores (based on factor analysis) > 1 SD	nonstandard	24	PP	50.3	Range: 30-63	5.4	Range: 1-21	37.50
(Dusankova, Kalincik, Havrdova, & Benedict, 2012)	1	10	2	1.50	fair		MACFIMS	369	RR, SP, PP, RP	34.0	10.0	8.0	7.0	55.00
(Faiss et al., 2014)	1	18	1	2.00	liberal		nonstandard	47	CIS	31.2	8.9	0.1	0.1	55.30
(Feinstein, Lapshin, O'Connor, & Lanctôt, 2013)	1	6	2	1.50	cons.		MACFIMS	144	RR, SP, PP	46.8	8.6	11.5	10.3	31.90
(Feuillet et al., 2007)	1	20	2	2.00	cons.		BRB-N + nonstandard	40	CIS	30.9	6.7	2.8	0.5	57.00
(Glanz et al., 2007)	1	8	1	1.50	liberal		BRB-N	92	CIS, MS	36.5	8.7	0.8	0.9	49.00
(Glanz et al., 2010)	1	8	1	1.50	liberal		BRB-N	92	CIS, RR	36.5	8.7	0.8	0.9	46.00
(Goretti et al., 2010)	1	10	2	2.00	cons.		BRB-N + Stroop	63	RR,SP	42.6	10.1	14.7	10.8	36.50
(Hulst et al., 2013)	1	5	2	2.00	cons.		nonstandard	55	RR, SP	48.0	7.1	11.7	7.0	36.40

Table e1. Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Publication	Strategy[1]	Number of	Critical	SD	Stringency[3]	Criteria specifics	Test battery[4]	N	Disease	Age		Disease duration		% CI[6]
(Inglese et al., 2008)	1	10	2	1.68	fair		nonstandard	32	RR, PP	51.1	Range: 29-71	6.5	Range: 1-34	56.30
(Jønsson et al., 2006)	2	30	N/A	(1.50)	N/A	2 out of 7 cognitive domain scores (average of associated normalized parameters) < -1.5 SD	nonstandard	80	RR, PP, SP	35.0	Range: 20-59	0.6	Range: 0.1-2	43.70
(Jønsson et al., 2006)	1	30	5	1.50	fair		nonstandard	80	RR, PP, SP	35.0	Range: 20-59	0.6	Range: 0.1-2	47.50
(Khalil et al., 2011)	2	9	N/A	(1.68)	N/A	1 out of 4 cognitive domain scores (average of associated normalized parameters) < -1.68	BRB-N	44	CIS	33.9	10.0	Median: 0.2	N/A	18.20
(Lapshin, Lanctôt, O'Connor, & Feinstein, 2013)	1	10	2	1.50	fair		MACFIMS	96	RR, SP, PP	48.5	9.8	11.3	8.5	41.70
(Lazeron et al., 2005)	3	6	(2)	(2.00)	N/A	1) composite score (sum of normalized parameters < -0.33 SD); or 2) two or more parameters below 2 SD	BRB-N	82	RR, SP, PP	47.0	Range: 27-73	10.5	Range: 1-27	67.00
(Leone et al., 2013)	1	9	3	1.68	cons.		BRB-N + Stroop	61	CIS, RR, SP, PP	43.9	11.8	13.3	9.5	47.50
(Marrie, Chelune, Miller, & Cohen, 2005)	1	7	1	1.68	fair		WAIS-III, WMS-III	136	RR, SP, PP	45.4	8.7	N/A	N/A	56.00
(Marrie, Miller, Chelune, & Cohen, 2003)	1	7	1	1.68	fair		WAIS-III, WMS-III	136	RR, SP, PP	42.4	13.7	7.1	10.0	56.00
(Mathiesen et al., 2006)	2	29	N/A	(1.50)	N/A	1.5 SD cut-off on composite score (sum of those normalized parameters that highly intercorrelate [Cronbach alpha=.76] and have a mean below T=50)	nonstandard	20	RR	36.0	8.0	<5	N/A	45.00
(Mesaros et al., 2009)	1	13	3	2.00	cons.		nonstandard	54	bMS	46.4	Range: 35-63	22.5	Range: 15-39	17.00
(Mesaros et al., 2012)	1	8	(2)	1.5; 2	N/A	1) 1 parameter ≥2SD and another ≥1.5 SD; or 2) 3 parameters ≥1.5 SD	BRB-N	82	RR, SP, PP, bMS	44.0	Range: 22-60	12.1	Range: 1-40	40.20
(Nocentini et al., 2006)	1	8	2	1.65	cons.		MDB	461	RR	35.9	8.4	Median: 6.3	N/A	31.00
(Nocentini et al., 2014)	1	13	2	1.68	fair		nonstandard	18	RR, SP	41.4	9.8	15.0	7.0	55.56
(Parmenter &	1	10	2	1.50	fair		MACFIMS w/o SDMT	100	RR, SP	44.6	8.4	N/A	N/A	55.00

Table e1. Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Publication	Strategy[1]	Number of	Critical	SD	Stringency[3]	Criteria specifics	Test battery[4]	N	Disease	Age		Disease duration		% CI[6]
Weinstock-Guttman, 2007)														
(Patti et al., 2009)	1	10	3	1.00	fair		BRB-N + Stroop	550	RR	33.4	8.3	5.0	5.3	22.00
(Penny et al., 2013)	1	13	2	1.68	fair		nonstandard	61	CIS, RR, SP	40.4	Range: 25-57	6.9	Range: 5-10	29.80
(Penny, Khaleeli, Cipolotti, Thompson, & Ron, 2010)	1	12	3	2.00	cons.		nonstandard	31	PP	51.0	Range: 11-18	8.9	Range: 7-12	29.00
(Portaccio et al., 2006)	1	9	1	2.00	cons.		BRB-N	41	RR	35.1	8.6	4.0	2.8	56.10
(Portaccio et al., 2009)	1	10	2	2.00	cons.		BRB-N + Stroop	85	RR	43.0	8.4	15.8	9.6	33.00
(Potagas et al., 2008)	1	9	3	1.68	cons.		BRB-N	160	MS	38.5	9.0	6.8	4.9	52.80
(Riccitelli et al., 2011)	1	7	2	2.00	cons.		nonstandard	73	RR, SP, PP	42.7	Range: 22-63	11.2	Range: 1-39	53.00
(Rocca et al., 2010)	1	11	3	2.00	cons.		nonstandard	16	PP	49.7	Range: 39-68	10.0	Range: 4-21	37.00
(Rossi et al., 2012)	1	8	2	2.00	cons.		BRB-N	142	RR	39.4	9.1	11.0	9.8	25.35
(Rosti, Hämäläinen, Koivisto, & Hokkanen, 2007)	1	34	7	1.68	cons.		nonstandard	45	RR	42.7	8.3	N/A	N/A	42.22
(Rovaris et al., 2002)	1	10	(3)	2.00	N/A	Abnormal parameters in at least two out of five different cognitive domains	nonstandard	34	RR	34.8	7.5	6.5	Range: 1-20	26.50
(Ruet et al., 2013)	1	10	2	1.50	fair		BRB-N + SR	65	RR	39.0	10.4	2.6	3.2	52.30
(Sánchez et al., 2008)	2	22	N/A	(1.68)	N/A	5th percentile cut-off on composite score (grading system for each parameter: 1-2 SD below normative mean [=1], more than 2 SD [=2])	nonstandard	52	RR	31.7	8.4	2.9	2.5	40.00
(Sayao, Bueno, Devonshire, & Tremlett, 2011)	1	5	2	1.68	cons.		NSBMS	47	bMS	27.7	7.4	27.2	1.8	17.00
(Simioni et al., 2007)	1	13	1	2.00	fair		nonstandard	106	CIS, MS	34.1	9.3	2.6	1.8	29.30
(Smestad et	1	15	(2)	1.50	N/A	Abnormal parameters in at least	nonstandard	84	MS	61.8	Range:	34.5	Range:	48.00

Table e1. Reviewed studies for classification criteria of cognitive impairment in Multiple Sclerosis

Publication	Strategy[1]	Number of	Critical	SD	Stringency[3]	Criteria specifics	Test battery[4]	N	Disease	Age		Disease duration		% CI[6]
al., 2010)						two of the four main functional areas (psychomotor speed, attention, memory, executive)				45-84		27-62		
(Till et al., 2011)	1	16	3	1.50	fair		nonstandard	35	MS	16.4	2.4	4.3	3.1	29.40
(Weinges-Evers et al., 2010)	2	10	N/A	(1.68)	N/A	Composite score (average of normalized parameters) < -1.68 SD	BRB-N + FST	109	RR	39.3	8.8	2.9	2.4	5.50
(Younes et al., 2007)	1	18	1	2.05	liberal		nonstandard	40	RR, SP, RP, PP	45.0	10.2	10.0	7.4	46.00
(Zipoli et al., 2010)	1	10	2	2.00	cons.		BRB-N + Stroop	56	CIS	33.2	8.5	0.0	0.0	25.00
(Zipoli et al., 2010)	1	10	3	2.00	cons.		BRB-N + Stroop	56	CIS	33.2	8.5	0.0	0.0	14.00
(Zivadinov, De Masi, et al., 2001)	1	18	(2)	2.00	N/A	Abnormal parameters in at least two out of six different cognitive domains	nonstandard	63	RR	35.4	9.1	5.8	3.3	23.80
(Zivadinov, Sepcic, et al., 2001)	1	18	(2)	2.00	N/A	Abnormal parameters in at least two out of six different cognitive domains	nonstandard	53	RR	30.2	9.4	3.8	1.3	26.40

1: Classification can be based on (1) the number of abnormal test parameters, (2) on the formation of a composite index, or (3) on a combination of the first two.

2: The number of cognitive parameters on which the classification criteria have been applied on

3: When possible the criteria were classified in respect of their stringency (liberal, fair, or conservative). This was based on false positive rates, i.e., on how many parameters healthy people fail on a cut-off of 1, 1.5, and 2 SD(Schretlen et al., 2008)*. Criteria were considered fair if CI was defined as performance below 1 SD on 32%±6.4%, on less than 25.6% as liberal, and on more than 38.4% as conservative. The respective figures were 17±3.4% for the 1.5 SD / 5th percentile cut-off, and 7.5±1.5% for the 2 SD cut-off.*

4: BRB-N = Brief Repeatable Battery of Neuropsychological Tests; CDT = Clock Drawing Test; FST = Faces Symbol Test; GAB = MindStreams GIobal Assessment Battery; MACFIMS = The Minimal Assessment of Cognitive Function in Multiple Sclerosis; MDB = Mental deterioration battery; NSBMS = Rao's Neuropsychological Screening Battery for MS; RIS=radiologically isolated syndrome; SDMT = Symbol Digit Modalities Test; SR = similarities subtest of the WAIS; Stroop = Stroop Test; VESPAR = Verbal and Spatial Reasoning Test; WAIS-III=Wechsler Adult Intelligence Scale, Third Edition; WCST = Wisconsin Card Sorting Test; WMS-III = Wechsler Memory Scale, Third Edition

5: RP=Relapsing Progressive PP=Primary Progressive MS; TP= Transitional Progressive MS; SP=Secondary Progressive MS; RR=Relapsing Remitting; CIS=Clinically isolated syndrome

6: Percentage of cognitive impairment

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Lebenslauf

Zum Schutz personenbezogener Daten wird in der elektronisch publizierten Version der Lebenslauf nicht veröffentlicht.

Liste wissenschaftlicher Veröffentlichungen

Zeitschriftenartikel

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Deutsche Zusammenfassung

Ziel der vorliegenden Dissertation war die Untersuchung etablierter und neuartiger Testverfahren zur Erfassung neurokognitiver Störungen bei Patienten mit Multiple Sklerose (MS). In drei Studien wurden folgende Fragestellungen beantwortet: (1): Welche Kriterien existieren für die Klassifikation einer kognitiven Störung bei MS und wie zuverlässig sind die daraus folgenden Ergebnisse in verschiedenen Krankheitsstadien? (2): Welche Gedächtnisstörungen lassen sich durch die Verwendung multipler Gedächtnistests und nach Berücksichtigung einer verlangsamten Verarbeitungsgeschwindigkeit in homogenen Gruppen mit jeweils früher oder später MS nachweisen? (3): Lassen sich durch die Verwendung eines neuartigen, auf der Theorie der Visuellen Aufmerksamkeit (TVA) basierenden Testverfahrens Defizite der visuellen Verarbeitungsfähigkeit in der Früh- und Spätphase der MS ermitteln und bestehen Zusammenhänge zu Defiziten in der konventionellen kognitiven Testung?

Zwei parallelisierte Gruppen mit insgesamt 77 MS Patienten wurden multizentrisch rekrutiert und mittels einer umfangreichen Batterie traditioneller neuropsychologischer Testverfahren, eines experimentellen, TVA-basierten Verfahrens (whole report) und mittels Magnetresonanztomographie untersucht. Erfasst wurden verschiedene Aspekte des verbalen und visuellen Gedächtnisses, quantitative und qualitative Aspekte der Informationsverarbeitungsgeschwindigkeit, visuell-konstruktive Fähigkeiten, vier TVA-basierte Parameter der visuellen Verarbeitungsfähigkeit, sowie hippokampales Volumen, Gesamthirnvolumen, kortikale Dicke und T1/T2 Läsionsvolumina. Zusätzlich wurde ein systematisches Review über verwendete Klassifikationskriterien durchgeführt und es wurden zwei parallelisierte Kontrollgruppen mit insgesamt 75 Probanden auf gleiche Weise neuropsychologisch untersucht wie die Patienten.

Im Rahmen des systematischen Reviews konnte gezeigt werden, dass in der Literatur verschiedenste Kriterien für die Definition einer kognitiven Störung bei MS Anwendung finden. Diese können zu beträchtlichen Klassifikationsunterschieden in Hinblick auf die Prävalenzrate führen. Außerdem ließ sich in der Literatur ein signifikanter Zusammenhang

zwischen der Schärfe des ausgewählten Kriteriums und der Erkrankungsdauer der untersuchten Stichprobe nachweisen.

Reduzierte Gedächtnisleistungen fanden sich über alle eingesetzten Testverfahren hinweg in der Gruppe mit später MS, jedoch in keinem Test in der Gruppe mit früher MS. In der Spätphase fanden sich zudem Zusammenhänge zwischen Gedächtnisdefiziten und Einbußen in der Verarbeitungsgeschwindigkeit. Nach statistischer Kontrolle des Einflusses der Verarbeitungsgeschwindigkeit war ein Zusammenhang zwischen hippokampaler Atrophie und Defiziten im verbalen Gedächtnis nachweisbar. Defizite im visuellen Gedächtnis waren hingegen mit kortikaler Dicke assoziiert.

In der kognitiv weitestgehend unbeeinträchtigten Gruppe mit früher MS ließen sich mittels TVA-basierter Testung Defizite der visuellen Verarbeitungsfähigkeit nachweisen. In der Spätphase waren die Defizite quantitativ und qualitativ stärker ausgeprägt. Die ausschließlich in der Spätphase auftretende Erhöhung der visuellen Wahrnehmungsschwelle wies darüber hinaus Zusammenhänge mit Markern der allgemeinen Krankheitsprogression, Defiziten des visuellen Gedächtnisses und der Informationsverarbeitungsgeschwindigkeit auf.

Die Ergebnisse legen nahe, dass es durch die Verwendung unterschiedlicher Klassifikationskriterien zu einer Überschätzung früher kognitiver Störungen gekommen sein könnte. Außerdem scheinen Gedächtnisstörungen vor allem im späteren Krankheitsverlauf, in relativ unspezifischer Form prävalent zu werden und teilweise auf eine verlangsamte Verarbeitungsgeschwindigkeit zurückzuführen zu sein. Schließlich könnten sich frühe Anzeichen kognitiver Veränderungen mittels TVA-basierter Testung aufdecken lassen und die Testung im späteren Krankheitsverlauf eine grobe Abschätzung kognitiver Defizite ermöglichen.

Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die geltende Promotionsordnung bekannt ist und ich die Dissertation selbst angefertigt habe, keine Textabschnitte eines Dritten oder eigener Prüfungsarbeiten ohne Kennzeichnung übernommen und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben habe. Die Auswahl und Auswertung des Materials sowie die Herstellung des Manuskripts habe ich selbstständig vorgenommen. Die Hilfe eines Promotionsberaters habe ich nicht in Anspruch genommen und Dritte haben weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Dissertation habe ich noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht. Ich habe weder die gleiche, noch eine in wesentlichen Teilen ähnliche, oder eine andere Abhandlung bei einer anderen Hochschule bzw. anderen Fakultät als Dissertation eingereicht .

Ort, Datum, Unterschrift