Neuropsychological Assessment in Multiple Sclerosis

An Overview

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Abstract: Neuropsychological deficits in multiple sclerosis (MS) are common. Over the past decades, many different procedures have been employed in diagnosing these deficits. Even though certain aspects of cognitive performance such as information processing speed and working memory may be affected more frequently than other cognitive functions, no specific deficit profile has been established in MS. This article provides an overview of the neuropsychological diagnostic procedures in MS and allows the reader to reach an informed decision on the applicability of specific procedures and the availability of study data in the context of MS. Additionally, it makes recommendations on the compilation of both screening procedures and extensive test batteries.

Keywords: Multiple sclerosis, neuropsychological diagnosis, cognitive screening, MACFIMS, PASAT, SDMT

Introduction

Clinical Presentation

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by lesions or plaques in the brain as well as in the spinal cord. It is one of the most common neurological diseases, with a peak onset age during early adulthood from about 20 to 40 years. Women are affected about twice as often as men. Inflammatory demyelinating processes affecting the myelin sheaths lead to axonal damage, which is progressive over the course of the disease. This in turn leads to various motor, autonomous, sensory, psychopathological, and cognitive dysfunctions.

Three separable forms of MS have been described: (1) In relapsing-remitting MS (RRMS), patients experience periods of exacerbated symptoms, followed by complete or incomplete remission of the symptoms after such an episode. (2) Approximately 80% of patients with relapsing-remitting MS develop a secondary-progressive (SPMS) variant over the course of the disease, (2a) which is characterized by a continuous decline of symptoms and (2b) may also be accompanied by acute episodes of exacerbated symptoms, which may or may not remit after the episode. (3) Finally, the chronic-progressive or primary-progressive (PPMS) disease form is characterized by a continuous worsening of symptoms without any episodes of symptom exacerbation (please refer to Appendix 1 for a list of abbreviations).

Neuropsychological Symptoms

Neuropsychological deficits are common in patients with multiple sclerosis. They occur in about 43–65% of patients (Bobholz & Rao, 2003; Benedict et al., 2006; McIntosh-
Affective neuropsychological functions are subject to a great variability, with some patients showing only mild and sporadic symptoms, while others suffer from extensive cognitive dysfunction. Thus, incidence rates and severity of cognitive deficits may vary widely. The following factors are thought to have an influence on the clinical presentation of cognitive deficits:

- First, while cognitive deficits occur both in relapsing-remitting as well as in chronic-progressive patients, several studies indicate a more pronounced cognitive impairment in patients with secondary-progressive as well as chronic-progressive disease (Beatty et al., 1995c; Greim & Zettl, 2009; Potagas et al., 2008).
- Second, although cognitive impairment may occur at any stage of the disease (DeSousa, Albert, & Kalman, 2002), severity of symptoms is loosely associated with duration of disease (Amato, Zipoli, & Portaccio, 2006).
- Third, even though it is weak, there is a consistent relationship between cortical lesion load as visualized by magnetic resonance imaging (MRI) scans and cognitive impairment (Comi, Rovaris, Leocani, Martinelli, & Filippi, 2000; Swirsky-Sacchetti et al., 1992).
- Finally, it has been reported that male MS patients suffer from cognitive dysfunction more frequently than their female counterparts (Beatty & Aupperle, 2002; Savettieri et al., 2004).

Because of the variety of possible neurological and neuropsychological deficits, general measures of neurological disability such as the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) have proved to be insufficient predictors for cognitive dysfunction. The EDSS assesses several motor and autonomous functions through clinical tests, observations, and self-reports, while neuropsychological deficits are virtually neglected (Rao et al., 1991; Ron, Callanan, & Warrington, 1991).

Axonal damage in MS may generally occur anywhere in the central nervous system (CNS), giving rise to many constellations of neuropsychological deficits. Cognitive functions found to be deficient in MS include attention and information processing speed (Achiron & Barak, 2003; Demaree, DeLuca, Gaudino, & Diamond, 1999; Piras et al., 2003), executive functions (Foong et al., 1997; Lazzaroni, Rombout, Scheltens, Polman, & Barkhof, 2004; Swirsky-Sacchetti et al., 1992) as well as verbal (Calabrese, 2006; Rao, Leo & Aubin-Faubert, 1989b) and nonverbal long-term memory (Greim & Zettl, 2009; Van den Burg, Van Zomeren, Minderhoud, Prange, & Meijer, 1987). On the other hand, general intelligence seems to be largely unaffected in MS (Chiaravalloti & DeLuca, 2008), and complete cognitive decline as is found in dementias is seen only rarely (Fischer, 2001). Also, agnosia, aphasia, and apraxia are not typically found in MS, and measures of short-term memory are almost uniformly reported as being unimpaired (Anzola et al., 1990; Rao, 1990b). Therefore, in most cases, symptom constellations in MS can be described as the combination of subtle cognitive deficits. Consequently, a neuropsychological examination should cover a broad spectrum of cognitive abilities.

**Influence of Depression and Fatigue**

It is also necessary to consider the impact of other disease-related factors such as depression and fatigue. Depression is commonly considered to have a moderate to considerable impact on several cognitive functions (Beblo et al., 2006; Veiel, 1997). The base-rate of developing a depression over the course of the disease lies at approximately 50% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987; Minden & Schiffer, 1991), considerably higher than in the general population. Even though the effects of depression on cognition in MS are still being discussed controversially (Arnett, Barwick & Beeney, 2008; Möller, Wiedemann, Rohde, Backmund, & Sonntag, 1994), several studies report such an association (Arnett, 2005; Thornton & Raz, 1997).

Fatigue, on the other hand, is being reported to be one of the most debilitating and most common symptoms in MS (Shah, 2009), whereby one must differentiate between physical and cognitive fatigue: While physical (or somatic) fatigue has been shown to be associated with parameters of physical endurance (Burschka et al., 2012), to date cognitive fatigue could not be associated with cognitive dysfunction beyond reasonable doubt (Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Krupp & Elkins, 2000). It has been reported that cognitive fatigue might be associated with decreasing performance in tasks of sustained attention (Krupp & Elkins, 2000), though to our knowledge, all attempts at objectifying symptoms of cognitive fatigue have failed to produce reliable results.

**Neuropsychological Examination**

Since the initial symptoms of the disease often manifest during early adulthood, when educational and vocational status are still in a state of flux, cognitive dysfunction can be an important predictor for psychosocial problems as well as quality of life over the course of the disease. Neuropsychological assessment is therefore required and should be an integral and early part of the diagnostic process in patients with MS or probable MS.

There has been much research and debate on the constellation of such a neuropsychological assessment, beginning with early – rather descriptive – studies on the nature of cognitive functions in MS (Demaree et al., 2003; Demaree, DeLuca, & Duval, 2004). The purpose of such a neuropsychological examination is to cover a broad spectrum of cognitive abilities, which may vary widely from patient to patient, and to provide an overall profile of cognitive functions that can be used to guide further medical and rehabilitative interventions.
of cognitive deficits in MS by Matthews, Cleeland, and Hopper (1970) as well as Reitan, Reed, and Dyken (1971). Thereafter, Rao (1990b) developed the Brief Repeatable Battery (BRB) of neuropsychological tests, which served as a foundation for standardized diagnosis.

Recent years saw the development of both extensive neuropsychological test batteries such as the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS, Benedict et al., 2006) as well as short screening procedures such as the Brief International Cognitive Assessment for MS (BICAMS, Langdon et al., 2012) and a shortened version of Rao’s BRB (Portaccio et al., 2009). These test batteries endeavor to make neuropsychological testing in MS more valid, reliable, and economic, while at the same time trying to cover the basic cognitive domains affected most often in MS. They are being employed internationally by numerous clinical institutions. Though their approach is promising, they are still in the process of being validated (e.g., Hansen et al., 2015; Portaccio et al., 2010; Sonder, Burggraff, Knol, Polman, & Uitdehaag, 2014). Also, their inventors acknowledge that international norms are still lacking for many of these test batteries (Benedict et al., 2012). One reason for the separate approach to neuropsychological assessment may be seen in the large variability of possible symptom constellations in MS. Cognitive functions may range from completely preserved to severely impaired. It is therefore sensible to first assess whether cognitive deficits are present and then if necessary establish an individual neuropsychological profile. Although no specific neuropsychological deficit profile can generally be associated with MS, a predilection for impaired information processing speed is being discussed in the contemporary literature (Chiara-valloti & DeLuca, 2008; Forn, Belenguer, Parcet-Ibars, & Ávila, 2008; Hoffmann, Tittgemeyer, & von Cramon, 2007). This is likely associated with cortico-cortical disconnections, which in turn may also affect other cognitive functions such as memory and executive functions.

The increasingly popular approach of using predefined test batteries for diagnosing cognitive deficits in MS, however, should not blind the clinical neuropsychologist to the applicability of other psychometric tests not included in such test batteries. A predefined screening or testing procedure cannot assess every cognitive ability possibly affected in MS patients. Therefore, a profound knowledge of available specific tests for assessing neuropsychological functions affected in MS is vital to enable the diagnostician to make an informed decision on which procedure to apply.

This article provides a comprehensive overview of neuropsychological functions found deficient in MS patients as well as tests suitable to assessing them. We consider both the above-mentioned, established test batteries and screening procedures as well as other diagnostic procedures found in the literature to diagnose cognitive deficits in MS patients. This article aims to enable the reader to make an informed decision on the suitability of such procedures in the context of neuropsychological assessment in MS.

**Measures of Attention and Psychomotor Speed**

Since basic attention can be subdivided into several constructs, many approaches have been applied toward the assessment of such deficits in MS patients. Many of these approaches have merit, though each highlights different aspects of attention. Impaired processing speed has been found to be a core deficit in MS, and patients tend to overreact adequately if information is presented sufficiently slow (Archibald & Fisk, 2000; Demaree et al., 1999; Kail, 1998). This finding is understandable if one considers that the rate of information processing speed relies heavily on cortico-cortical connections in the white matter, which tend to be affected with growing lesion load (Fisk & Archibald, 2001).

In the next section, we consider both computerized as well as pen-and-paper-based tests. However, both the Symbol Digit Modalities Test (SDMT, Smith, 1982) as well as the Paced Auditory Serial Addition Test (PASAT, Strauss, Sherman, & Spreen, 2006) have been shown to be the most extensive use in MS and are discussed separately. An overview of the considered testing procedures can be seen in Table 1.

**Symbol Digit Modalities Test**

The Symbol Digit Modalities Test (SDMT) (Smith, 1982) is perhaps the only instrument most often used in the neuropsychological assessment of MS patients. It is a simple test of basic attention and psychomotor speed. The patient has to verbally pair numbers and symbols according to a fixed pattern, the outcome score reflecting the number of patterns solved within 90 seconds. There is a written and an oral version of this test, but the oral version has been shown to be wider use in MS. This is probably mainly because impairments of motor function in advanced MS stages might otherwise impair performance. The SDMT has been used in neuropsychological test batteries for almost three decades (Franklin, Heaton, Nelson, Filley, & Seibert, 1988) and continues to be an integral part of the Brief International Cognitive Assessment for MS (BICAMS, Langdon et al., 2012), the Minimal Assessment of Cognitive Function in MS (MACFIMS, Benedict et al., 2002), and the Brief Repeatable Battery (BRB, Rao et al., 1991). Lately, it was claimed to be the one cognitive screening tool with the best predictive value for
<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Cognitive subfunction</th>
<th>Strengths and weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>Smith (1982)</td>
<td>attention information processing speed</td>
<td>+ brevity + high prognostic validity + well accepted by patients + no fine-motor functions required + extensively researched in MS + parallel forms exist – possible confounding through visuospatial ability</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>Strauss et al. (2006)</td>
<td>divided attention working memory information processing speed</td>
<td>+ differentiates well between cognitively impaired and preserved patients + brevity + no fine-motor functions required + extensively researched in MS + parallel forms exist – possible confounding with mathematical ability – still unclear which cognitive function constitutes the main aspect of PASAT performance – stressful and demanding – frequently rejected by patients</td>
</tr>
<tr>
<td>Paced Visual Serial Addition Test (PVSAT)</td>
<td>Diamond et al. (1997)</td>
<td>visual information processing speed</td>
<td>+ visual alternative to the PASAT – minimal relevant study data</td>
</tr>
<tr>
<td>Digit-symbol coding (WAIS-IV)</td>
<td>Wechsler (2008)</td>
<td>psychomotor speed attention</td>
<td>+ alternative to the SDMT – minimal relevant study data – less suitable than the SDMT because of confounding with motor dysfunctions</td>
</tr>
<tr>
<td>Testbatterie zur Aufmerksamkeitsprüfung (TAP)</td>
<td>Zimmermann &amp; Fimm (2009)</td>
<td>several aspects of intrinsic and selective attention</td>
<td>+ allows a differentiated diagnostic of attentional systems + can be employed for specific questions pertaining to the functioning of the attentional system + less expensive than other computerized tests – limited study data in MS – motor as well as visual dysfunction are possible confounding factors</td>
</tr>
<tr>
<td>Wiener Testsystem (Vienna System), i.e., ‘Determinationstest’, ‘Reaktionstest’</td>
<td>Schuhfried (1992)</td>
<td>several aspects of intrinsic and selective attention</td>
<td>+/- strengths and weaknesses are analogous to the TAP, though even less literature pertaining to MS exists for the Vienna System</td>
</tr>
<tr>
<td>Attention Network Test (ANT)</td>
<td>Fan et al. (2002)</td>
<td>several aspects of attention, including alertness, orienting, and executive control</td>
<td>+ assessment of several attentional processes in one subtest – very limited study data available</td>
</tr>
<tr>
<td>Faces Symbol Test (FST)</td>
<td>Scherer et al. (2007)</td>
<td>concentration and attention working memory</td>
<td>+ specifically designed for screening in MS – very limited study data available</td>
</tr>
<tr>
<td>Trail-Making Test (TMT)</td>
<td>Reitan (1955)</td>
<td>processing speed visuomotor tracking cognitive flexibility divided attention</td>
<td>+ extensive norms available + self-paced – motor dysfunctions are a confounding factor – influence of psychomotor speed on cognitive flexibility is unclear</td>
</tr>
<tr>
<td>d2</td>
<td>Brickenkamp et al. (2010)</td>
<td>attention (both intensity and selectivity aspects)</td>
<td>+ extensive norms available – confounding with visuospatial processing – confounding with motor dysfunctions – little relevant study data in MS</td>
</tr>
<tr>
<td>Stroop Test (ST)</td>
<td>Bäumer (1985)</td>
<td>attention processing speed cognitive flexibility</td>
<td>+ some validation data exist in MS +/- contemporary studies see its usefulness more in the field of executive function – confounding with visuospatial deficits</td>
</tr>
<tr>
<td>Verbal and Nonverbal Digit Span (WMS)</td>
<td>Härtling (2000)</td>
<td>attention short term memory</td>
<td>+ some validation data exist in MS +/- most studies report that MS patients are unimpaired on these measures</td>
</tr>
<tr>
<td>brief test of attention (BTA)</td>
<td>Schretlen et al. (1996)</td>
<td>selective (divided) attention</td>
<td>+ supposedly indicative of cortico-cortical disconnections + some study data exist – little validation data available in an MS population</td>
</tr>
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cognitive dysfunction in MS (Sonder et al., 2014). However, as Hansen et al. (2015) pointed out, the predictive value of the SDMT alone is limited, and using it as a single outcome measure is therefore not advisable.

Because of its brevity, its well-established norms (Smith, 1982), its user friendliness, and its independence of fine-motor skills, it has often been proposed in recent years to be the preferable measure for basic attention in MS (Battista et al., 2012; Benedict et al., 2012; Benedict et al., 2017; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007b). Also, it has been pointed out that there is a strong association of SDMT scores with central cortical atrophy as visualized by neuroimaging techniques (Christodoulou et al., 2003). Possible confounding factors exist with visual or visuoperceptive impairments.

A similar test that has also seen use – although a lot less frequently – in diagnosing MS patients is the subtest “digit-symbol coding” of the Wechsler Adult Intelligence Scale (WAIS, Andrade et al., 1999; Drew, Tippett, Starkey, & Isler, 2008). However, since digit-symbol coding requires fine motor skills, the SDMT is considered preferable.

**Paced Auditory Serial Addition Test**

The Paced Auditory Serial Addition Test (PASAT) is a measure of information processing speed, working memory, and divided attention (Strauss et al., 2006). According to some researchers, it is also considered to be a valid tool for assessing executive function (Hansen et al., 2017), but its requirements concerning attention and psychomotor speed are undisputed (Forn et al., 2008). Problems in the PASAT seem to be correlated mainly with processing speed and less so with working memory impairments (Lengenfelder et al., 2006; Lynch, Dickerson, & Denney, 2010).

Here, numbers are read to the patient with an interstimulus interval (ISI) of 3 seconds. The patient adds each number to the one immediately prior to it. The outcome score is the number of correct calculations. Versions with differing ISIs exist (Gronwall, 1977), but the 3-second ISI has become the benchmark in the diagnosis of cognitive dysfunction in MS (Benedict et al., 2002; Rao et al., 1991).

The PASAT is – along with the SDMT – one of the most widely used diagnostic instruments in MS. Not only is it part of the Brief Repeatable Battery (BRB, Rao et al., 1991) and other neuropsychological test batteries (Peyser, Rao, LaRocca, & Kaplan, 1990), it is also an integral part of the Multiple Sclerosis Functional Composite Score (MSFC, Fischer, Rudick, Cutter, & Reingold, 1999), which was developed to assess clinical parameters of disability in MS.

Even though the PASAT still sees regular use in MS (Bodden & Kalbe, 2010; Glanz et al., 2007; Rosti, Hamalainen, Koivisto & Hokkanen, 2007) and is considered an important part of cognitive screening in MS (Langdon, 2010), it has often been criticized. Criticism mainly focused on the fact that the PASAT requires a certain amount of mathematical ability and might therefore be confounded with this ability (Rogers & Panegyres, 2007; Sandry, Paxton, & Sumowski, 2016). Also, patients tend to perceive the task as too stressful and might therefore be impaired in their performance without in fact suffering from cognitive deficits (Fisk & Archibald, 2001).

A nonverbal version of this test is called the Paced Serial Addition Test (PVSAT, Diamond, DeLuca, Kim, & Kelley, 1997), which has also been employed occasionally in MS-related studies, mainly to assess differences between auditory and visual information processing (Staf fen et al., 2002).

**Computerized Tests of Attention**

Perhaps surprisingly, only a relatively small number of studies have employed computerized tests of attention in the diagnosis of cognitive dysfunction in MS. Even though simple reaction time tasks comparable to an Alertness paradigm as well as complex two-choice reaction time tasks essentially representing a Go-NoGo paradigm have been employed in the diagnosis of cognitive dysfunction in MS for quite some time (Rao et al., 1989b), none of these tests found entry into the frequently used neuropsychological test batteries. In past decades, this might have been explained by the fact that a computerized test necessarily requires a lot of encumbering equipment and might thus not have been feasible in a clinical setting. Also, these instruments tended to be expensive, which might have appeared uneconomic. Nowadays, however, these arguments appear outdated. More relevant is the fact that they necessarily rely on motor speed, making physical disability a possible confounding factor. Thus, many authors prefer to merely employ the SDMT as a single predictor of basic attention. Nonetheless, some authors have made the effort to integrate computerized tests into their neuropsychological assessment procedures in MS. Among the instruments used is the Testbatterie zur Aufmerksamkeitsprüfung (TAP, Test battery of attentional performance Fischer et al., 2014; Hansen et al., 2015; Penner, Rausch, Hardmeier, Kappos, & Radü, 2001; Schulz, Kopp, Kunkel, & Faiss, 2006), which consists of a number of subtests assessing different attentional constructs (Zimmermann & Fimm, 2009). The subtests employed vary from study to study, but there is consensus on using the subtests “Alertness” and “Divided Attention”. Other subtests regularly applied include the “Go-NoGo” and “Flexibility” paradigms as well as “Working Memory.” Recent studies on cognition in MS employing a number or all of these subtests include
research by Brien et al. (2014), Hansen et al. (2015), Kunkel et al. (2015); Pöttgen et al. (2015a, 2015b), and Keune et al. (submitted). Also, a study by Olivares et al. (2005) reported significantly slower reaction times of MS patients compared to a control group on the simple and selective attention tasks of the Vienna System (Schuhfried, 1992), a computer program not unlike the TAP. The merit of such computerized tests of attention is that evaluation of results is processed automatically and administration of tests is easy. After explaining the test paradigm to the patient, tester leaves the task to be handled autonomously by the patient. Furthermore, since each subtest covers a different aspect of attentional performance, the TAP allows for a comprehensive check of cognitive functioning in the field of attention. Plohmann et al. (1998) grouped MS patients into distinct subgroups with varying levels of attentional deficits according to their profiles on six different subtests of the TAP. Besides, as at least some studies have pointed out (Küst & Dettmers, 2014; Schultheis, Garay, & DeLuca, 2001), the cognitive deficits associated with MS may exert an influence on a patient’s performance when driving a car. Such possible negative influences should also be evaluated by a comprehensive diagnostic procedure, which necessitates a computerized test battery (Schale & Küst, 2009).

Although there may be a confounding effect of deficient motor control in further progressed MS, Hansen et al. (2015) consider the TAP subtests Alertness, Go-NoGo, and Divided Attention to be procedures of choice when assessing attentional performance in MS, and Calabrese (2003) explicitly suggested the TAP for diagnosis. The developers of the TAP (Zimmermann & Fimm, 2009) also considered this test constellation to be the minimal assessment of attentional performance. Heesen et al. (2010) also demonstrated the sensitivity of the TAP in conjunction with other neuropsychological measures when diagnosing cognitive deficits in MS. Special emphasis should be put on the performance in the more complex tasks “Divided Attention” and “Flexibility,” since deficits in divided attention and alternating attention appear to be deficient most frequently in MS (Archibald & Fisk, 2000; D’Esposito et al., 1996; Grigsby, Kaye, & Busenbark, 1994).

Other computerized tests of attention that have been employed in the diagnosis of MS include the Attention Network Test (ANT, Fan, Candlliss, Sommer, Raz, & Posner, 2002). The ANT supposedly assesses various component networks of attention (alerting, orienting, executive control) as originally postulated by Posner and Petersen (1990). A preliminary study by Ishigami, Fisk, Wojtowicz, and Klein (2013) concluded that a modified version of the ANT (Callejas, Lupíñez, Funes, & Tudela 2005) is a reliable tool for repeated testing in MS.

Another computerized test of attention is the Faces Symbol Test (FST), which was specifically developed to screen for cognitive dysfunction in MS by focusing on concentration and attention (Schier et al., 2007). Though early studies pointed toward a high validity of the procedure (Grabner et al., 2008), it was subsequently received rather critically (Williams, O’Rourke, Hutchinson, & Tubbidy 2006) and seems to have fallen in disuse since then.

### Pen-and-Paper Tests of Attention

Although SDMT and PASAT are considered to be the benchmark in assessing psychomotor speed and attention in MS, they fall short when assessing the complete width of attentional performance. Therefore, other procedures that focus on different aspects of attention may also have more merit in this respect.

In MS, an alternative procedure that has seen a lot of use is the Trail-Making Test (TMT, Reitan, 1955). This neuropsychological classic consists of two parts: In the first part (TMT-A), the patient connects numbers in sequential order; in the second part (TMT-B), the patient has to alternate between numbers and letters. The first part is considered to assess cognitive processing speed, scanning, and visuomotor tracking (Tombaugh, 2004; Lezak, 2012), whereas the second part is more indicative of deficient cognitive flexibility and divided attention (Lezak, 2012).

The TMT has been employed in the diagnosis of cognitive deficits in MS at least since the 1970s (Ivnik, 1978; Reitan et al., 1971) and still sees frequent use in contemporary neuropsychological studies focusing on MS (Amato et al., 2014; Ceresa et al., 2013). In contemporary studies, the TMT hardly appears as a critical outcome measure. However, since MS patients usually perform better or even without impairment on self-paced tests of attention with printed material in front of them (Beatty, Goodkin, Monson, & Beatty 1989; Kujala, Portin, Revonsuo, & Ruutiainen, 1994), and since deficits begin to show on easier tasks only when cognitive decline has progressed further, it remains a valuable diagnostic instrument. It should be taken into account that motor speed and agility are confounding factors on this test (Shum, McFarland, & Bain, 1990).

Another pen-and-paper-based test of attention that has been mentioned as an adequate tool for assessment in MS, is the “Aufmerksamkeits-Belastungs-Test” (d2-R, attentiveness endurance test, Brickenkamp, Schmidt-Atzert, & Liepmann, 2010). Here, the patient reads through lines of the letters “p” and “d,” each marked with one to four dashes. The patient then marks each “d” with two dashes. Editing time is limited to 20 seconds per line. Wegener, Marx, and Zettl (2013) consider it to be a choice tool for assessing selective attention in a comprehensive neuropsychological test battery. It has also been proposed by...
other authors as a measure of attention (Bodden & Kalbe, 2010; Calabrese, 2003). However, study data in a MS population remains scarce so far, making its applicability and interpretability at least questionable.

Other Tests of Attention

Three other instruments focusing on attention should be mentioned here: the Stroop Test (ST, Bäumler & Stroop, 1985), the Verbal and Nonverbal Digit Span (e.g., Härtling et al., 2000), and the Brief Test of Attention (BTA, Schretlen, Bobholz, & Brandt, 1996). These are listed separately since they do not require the patient to make any notes or perform physical manipulations usually required of pen-and-paper-based tests. Therefore, they might be worth special consideration when testing patients with MS, who often exhibit motor dysfunctions.

The ST is a test of selective attention and cognitive processing speed as well as of cognitive inhibition as a measure of executive function. Therefore, it will also be discussed in the section below concerning executive functions. It consists of three conditions: In the first condition, patients read out color words (blue, green, red, yellow). In the second, ink-colored blocks are named appropriately. In the final condition, color words inked in another color than the one they are written in are presented. The patient names the color the words are inked in, thereby resisting the interfering tendency to read the written color (Lezak, 2012). Different conditions have been employed for different purposes. Rao et al. (1989b, 1991), for example, used the interference condition as a measure of attention and concentration. Peyer et al. (1990) also considered this variant as a valid assessment of attentional resources. Pujol et al. (2001) employed the word naming and the interference condition of the ST as a clinical correlate to medial frontal and posterior parietal lesions in MS. Results pointed toward the direction that right frontal demyelination led to a reduction of processing speed, while left posterior parietal demyelination was associated with reduced performance in the interference condition. Contemporary neuropsychological studies have employed the interference condition of the ST more as a measure of executive function and less for assessing attention (Amato et al., 2014; Cerasa et al., 2013; Chillemi et al., 2015).

Tests of auditory and visuospatial span used to be an integral part of neuropsychological test batteries (Franklin et al., 1988; Rao et al., 1991), both as a measure for attention as well as for immediate recall. However, most studies concluded that digit span is largely unimpaired in MS (Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Rao et al., 1991), even though some exceptions have been reported (Fischer, 1988; Beatty, Paul, Blanco, Hames, & Wilbanks, 1995b). Beatty et al. (1995b) also surmised that deficits in digit-span tasks in MS patients result from a generalized difficulty in maintaining concentration, making this procedure more indicative as a measure for attentional performance.

The BTA is a relatively recent addition to the growing pool of tests of attentional performance. It was developed by Schretlen et al. (1996) as a measure of auditory divided attention and is based on a model proposed by Cooley and Morris (1990). According to the developers of the BTA, successful performance of the task requires the continuous monitoring of two selective-attention tasks, resulting in the division of attention. Probably because similar processes have often been described as being deficient in MS as the consequence of cortico-cortical disconnections because of white-matter lesions (Fisk & Archibald, 2001), the BTA has been employed as an outcome measure in several clinical studies (Greene et al., 2000; Porcel & Montalban, 2006; Sherman, Rapport, & Ryan, 2008). Further research into the psychometric properties of the BTA is scarce, however, and it remains unclear whether it is equally suited for diagnosis as similar procedures like the PASAT.

An overview of the discussed procedures in this section may also be seen in Table 1.

Tests of Memory

Impaired memory functions are widespread in MS patients and represent another of the core cognitive deficits found in this disease (Rao et al., 1993). The neuroanatomical correlate for these deficits appears to be grey-matter atrophy in general (Calabrese, Filippi, & Gallo, 2010) and especially in hippocampal structures (Scicotte et al., 2008), which in turn may be attributed to neuronal loss and demyelination (Papadopoulos et al., 2009). Furthermore, connectivity of hippocampal regions with other brain areas appears to have a mediating influence on the severity of memory deficits (Hulst et al., 2014; Leavitt, Wylie, Genova, Chiaravalloti, & DeLuca, 2012). Also, reduced information processing speed appears to impact negatively on encoding capacities, resulting in deficient information acquisition (Lafose, Mitchell, Corboy, & Filley, 2013).

Explicit memory is most often deficient in MS patients. Affected memory functions include long-term memory (Rao et al., 1993) for both verbal and nonverbal materials, that is, the learning, retention, and recall of new information. Working memory, which relies heavily on an intact processing of information, has also often been found to be impaired (Parmenter, Shucard, & Shucard, 2007a) and is discussed in the section pertaining to executive functions. Remote memory and implicit memory seem to
be largely unaffected (Beatty et al., 1989; Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984), as is digit span (Rao et al., 1991). Again, an overview of the considered procedures may be found in Table 2.

### Tests of Verbal Memory

Two tests of verbal memory have been especially prominent in the recent literature on cognitive assessment in MS. The first is the Selective Reminding Test (SRT, Buschke & Fuld, 1974) which is an integral part of both the Brief Repeatable Battery (BRB) and a shortened form of the BRB, which was established recently (Hansen et al., 2015; Portaccio et al., 2009). The second one is the California Verbal Learning Test (CVLT, Niemann, Sturm, Thöne- Otto, & Willmes, 2008), which is an integral part of both the Brief Inventory for Cognitive Assessment in MS (BICAMS) as well as the Minimal Assessment of Cognitive Function in MS (MACFIMS). Since both are equally frequent in use, they are discussed in some detail.

#### Table 2. Procedures for assessing memory function.

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Cognitive subfunction</th>
<th>Strengths and weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Reminding Test (SRT)</td>
<td>Buschke &amp; Fuld (1974)</td>
<td>verbal memory</td>
<td>+ vast amount of study data exist in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(list learning, retention, recall)</td>
<td>+ good differentiation between cognitively preserved and impaired patients</td>
</tr>
<tr>
<td>California Verbal Learning Test (CVLT)</td>
<td>Niemann et al. (2008)</td>
<td>verbal memory</td>
<td>+ vast amount of study data exist in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(list learning, retention, recall)</td>
<td>+ good differentiation between cognitively preserved and impaired patients</td>
</tr>
<tr>
<td>Verbal Learning and Memory Test (VLMT)</td>
<td>Helmstaedter et al. (2001)</td>
<td>verbal memory</td>
<td>+ roughly similar alternative to the CVLT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(list learning, retention, recall)</td>
<td>+ no compelling argument against employing it in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– insufficient validation in MS</td>
</tr>
<tr>
<td>Logical Memory I &amp; II (WMS)</td>
<td>Härtling (2000)</td>
<td>verbal memory</td>
<td>+ sufficient validation in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(story learning and story recall)</td>
<td>+ differentiates between patients and healthy controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+/- assesses an inherently different construct than list learning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+/- patients tend to be less impaired on story recall than on list learning</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test – Revised (BVMT-R)</td>
<td>Benedict (1997)</td>
<td>nonverbal memory (learning and recall of abstract figures) visuospatial function</td>
<td>+ sufficient validation in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ good differentiation between patients and healthy controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ six parallel forms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+/- possible confounding with motor dysfunction is putatively controlled for by means of a copy trial</td>
</tr>
<tr>
<td>Spatial Recall Test (7/24 and 10/36)</td>
<td>Rao et al. (1984)</td>
<td>nonverbal memory (pattern learning and recall)</td>
<td>+ large amount of study data in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ sufficient validation in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– possible confounding factors with visuospatial ability, but also processing speed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– inferior to the BVMT concerning predictive value</td>
</tr>
<tr>
<td>Rey–Österrieth Complex Figure Test (ROCF)</td>
<td>Rey (1941), Österrieth (1944)</td>
<td>nonverbal memory (figure learning and recall) visuospatial ability</td>
<td>+ allows insight into various cognitive abilities, including executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– insufficient validation in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– differentiates less accurately than verbal memory tests between healthy controls and patients</td>
</tr>
</tbody>
</table>
unimpaired. Another study found evidence that recall and recognition is equivalent to that of healthy controls in a modified version of the SRT (Chiaravalloti, Balzano, Moore, & DeLuca, 2009). These results might be understood as validating the rationale to forego a measure of delayed recall when conducting a test of verbal memory in MS. They point toward the necessity to instead focus on measures of information acquisition.

The CVLT is also based on the paradigm of multiple trial list learning. Its outstanding feature is that it assesses the use of semantic associations as a strategy for learning, since the 16-item wordlist can be subdivided into four semantic categories. A comprehensive study by Stegen et al. (2010) found considerable impairments in a large group of MS patients, which pertained to most of 23 different scores in comparison to a healthy control group. Effect sizes greater than .85 were found for five scores: consolidation, primacy and recency effects, proactive interference, and learning asymptote. The highest effect size was found for free recall after interference. The authors concluded that MS patients are overwhelmed by the amount of information at first presentation. They show a distinct learning curve over recurring trials, albeit at a slower rate than healthy controls. Delayed recall did not range among the best predictors for memory impairment in MS. Again, this might be interpreted as an argument to refrain from also assessing delayed recall. In fact, execution of the CVLT in the BICAMS is limited to the five learning trials, interference list, and short delay free recall (Benedict et al., 2012). Stegen et al. (2010) also found evidence for the external validity of the CVLT, since a distinct difference between employed and work-disabled patients emerged in their study.

In summary, both tests are well suited to assessing impairments of verbal memory. A study by Strober et al. (2009) found that their sensitivity in predicting memory deficits in MS patients is about the same. Since both require an approximately equal amount of time, no final decision can be made on the superiority of one procedure over the other. As a final remark on these procedures, the statement that delayed recall of verbal material is less impaired than other aspects of verbal learning in MS (e.g., DeLuca et al., 1998; Stegen et al., 2010) is by no means undisputed. A meta-analysis by Prakash, Snoek, Lewis, Motl, and Kramer (2008), including 57 studies of cognitive decline in patients with relapsing-remitting MS, found moderate effects of disease on verbal and nonverbal immediate recall. However, the most pronounced effect of disease was reported on the delayed recall of verbal memory. This seeming contradiction is dissolved if one considers that deficient performance in delayed recall is strongly confounded with deficient performance during learning trials. Therefore, MS patients are worse than controls in acquiring information and consequently also recall less than controls after delay. However, different than in, say, Alzheimer’s dementia, they do not usually suffer from a significant loss of information during retention intervals. Thus, the amount of information recalled after the retention interval relative to the amount of information memorized during learning trials does not significantly differ from that of healthy controls.

Other procedures assessing verbal memory in MS include the Verbal Learning and Memory Test (VLMT, Helmsstaedter, Lendt & Lux, 2001) as well as the logical memory subtests of the Wechsler Memory Scale (WMS, Härtting et al., 2000). These are employed less often than the SRT and CVLT, so that less study data in MS exist on these procedures. Nonetheless, they may be viable alternatives to the better-established procedures:

The VLMT (also: AVLT) is the German version of the Rey Auditory Verbal Learning Test. Like the CVLT, it is a test of multiple trial list learning. Different from the CVLT, it does not include different semantic categories. This procedure has been employed often in the assessment of cognitive deficits in MS and continues to be a popular method in clinical outcome studies (e.g., Briken et al., 2014; Faiss et al., 2014; Fischer et al., 2014; Kolber et al., 2015). Penner et al. (2015) decided on the rationale of replacing the CVLT with the VLMT in the BICAMS. Their reasoning was that the VLMT norms consist of a larger sample and covers a wider age range. Results indicated that patients did not differ significantly from controls concerning learning trial performance. To our knowledge, a systematic comparison of CVLT and VLMT performance in MS patients has yet to be achieved. However, a study by Helmsstaedter, Wietzke, and Lutz (2009) compared performance on these two tests as well as the WMS subtest logical memory in a group of epilepsy patients. The authors concluded that the three tests should not be considered interchangeable because they put different demands on semantic processing and memory organization. Also, they are differentially sensitive to impaired performance in nonmemory domains. In sum, there is no evidence that the VLMT is less indicative of memory deficits in MS than the CVLT, and its application thus appears to be a valid approach because of more comprehensive norms in certain languages. However, interchangeability with the CVLT should not be taken for granted because the assessed memory functions cannot be considered completely redundant. Further research into this question is required.

The logical memory subtest of the WMS is a different approach to assessing verbal memory. Two short stories have to be recalled by patients immediately after their being read to them (logical memory I) and once again after an interval of approximately 30 Minutes (logical memory II). The test measures memory for contextual verbal material (Härtting et al., 2000). Several subtests of the WMS
have been incorporated into test batteries for cognitive function in MS, among those of logical memory (Clemmons, Fraser, Rosenbaum, Getter, & Johnson, 2004; Fischer, 1988; Peyser et al., 1990). They have been shown to be sensitive to memory and learning deficits, especially in the initial acquisition of information (Kujala, Portin, & Ruutuainen, 1997; Minden, Moes, Oray, Kaplan, & Reich, 1990; Olivares et al., 2005), and they differentiate between patients with deteriorated memory and preserved patients (Kujala, Portin, & Ruutuainen, 1997). Also, Rao, Leo, and Aubin-Faubert (1989a) found significant differences between MS patients and healthy controls on a story recall test similar to the logical memory-paradigm. Similar to findings on other tests of verbal memory, though MS patients recalled significantly less details than controls, retention did not differ significantly from that of the control group over an interval of 24 hours: MS patients recalled the main elements of the stories better than nonessential details, which conforms to the performance of healthy persons. In another study, their overall recall was also worse than that of controls (Lokken et al., 1999). Beauty (2004) compared list learning and story learning in MS patients. Results indicated that recall of wordlists was more impaired than story recall. A possible explanation might be that the “inherent meaningfulness of the passage provides a kind of ‘glue’ to help the material stick” (Strauss et al., 2006). In summary, story learning tests such as the WMS subtest logical memory seem to be indicative of memory deficits in MS but they measure a distinctly different aspect of verbal memory than list-learning tests.

**Tests of Nonverbal Memory**

In recent years, the Brief Visuospatial Memory Test – Revised (BVMT) has been featured very prominently in studies involving the cognitive assessment of MS patients (Benedict, 1997). It has been proposed both as part of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS, Benedict et al., 2002) as well as the BICAMS (Langdon et al., 2012). Six abstract designs are presented for 10 seconds, during which the patient memorizes them. After the display is removed, the patient draws the designs from memory. There are three learning trials and an optional delayed free recall after 20 Minutes. A recognition trial is also optional. Criterion-related validity appears to be good. Generally, MS patients appear to show poorer test performance on the BVMT than do healthy controls (Benedict, Priore, Miller, Munschauer, & Jacobs, 2001). In a study of 291 patients and a control group of 56, the BVMT discriminated MS patients from healthy controls and correctly identified cognitively impaired patients (Benedict et al., 2006). Gaines, Gavett, Lynch, Bakshi, and Benedict (2008) reported that MS patients scored systematically lower than controls on most parameters of the BVMT: Total Recall, Delayed Recall, and Recognition. They also reported that MS patients tended to produce intrusions and qualitative errors more often than controls. Test-retest-reliability was reported to be good ($r = 0.91$). Six different parallel forms of the test exist, making this instrument ideal for retesting. Study data suggests that interform reliability is acceptable (Benedict, 2005).

Another prominent procedure for assessing visual memory in MS is the Spatial Recall Test (Rao et al., 1984). Subjects are shown a checkerboard, the size of which varies depending on the applied variant of the procedure. The variant used in the BRB consists of 36 fields arranged on a 6 x 6 square, on which 10 checkers are randomly positioned (10/36). Another widely used variant consists of 24 squares and seven randomly positioned checkers (7/24). Just like in the BVMT, the subject memorizes the design over three learning trials; delayed recall is also assessed. Since the BRB has been applied in the assessment of cognitive dysfunction in MS for well over 20 years, many studies have employed the paradigm of the spatial recall test (Camp et al., 2005; Kujala et al., 1997; Rao et al., 1989a; Rao et al., 1991).

In a study by Gontkovsky, Vickery, and Beauty (2004), the study group of 64 MS patients performed considerably worse than the normative sample of the 7/24 test. Results of a factor analysis were interpreted such that the 7/24 is sensitive to general cognitive deficits in MS, but that there is only limited support for the hypothesis that the 7/24 is a valid measure of visuospatial learning and memory. On the contrary, factor analysis revealed that deficient results in the 7/24 were also explained by two additional factors interpreted as visuospatial perception and processing speed. Glanz et al. (2007), on the other hand, did not find significant differences between newly diagnosed MS patients and controls on the 10/36. Another study (Strober et al., 2009) compared two most prominent cognitive screenings in MS (BRB and BICAMS) and concluded that, by and large, the predictive value of both screenings is approximately equal. There was, however, one noteworthy exception when considering only those tests relevant for the assessment of nonverbal memory: The BVMT showed a better sensitivity than the 10/36. These results were reinforced by a recent replication study (Niccolai et al., 2015), which found considerable differences concerning the predictive value of BVMT and 10/36. These findings might help explain why the BVMT is often favored above the spatial recall test, even though the spatial recall test still sees considerable use as a clinical outcome parameter (Amato et al., 2014; Bonavita et al., 2015; Cerasa et al., 2013; Mattioli, Bellomi, Stampatori, Capra, & Miniussi, 2016a).

A third procedure that has seen extensive use in diagnosing deficits in nonverbal memory both in MS patients and
A very small number of studies have investigated remote memory tasks in MS. While Rao et al. (1991) did not find any significant differences between MS patients and healthy controls on the President’s Test (Caine, Bamford, Schiffer, Shoulson, & Levy, 1986), Beatty, Goodkin, Monson, Beatty, and Hertsgaard (1988) did report such differences in a group of chronic-progressive MS patients on both the President’s Test as well as the Famous Persons Test (Lezak, 2012). In a meta-analysis, Zakzanis (2000) concluded that performance of MS patients on these two tests was comparatively worse than on recognition memory tasks in comparison to healthy controls.

There is also a certain amount of evidence that autobiographical memory might be impaired both in secondary progressive as well as in relapsing-remitting MS, as two recent studies reported (Ernst et al., 2013; Müller et al., 2013). Both studies employed the Autobiographic Memory Interview by Kopelman, Wilson, and Baddeley (1989). The former study also used the Modified Crotvit Test (Graham & Hodges, 1997), which is a cue-word paradigm.

However, because of the very limited number of studies on remote or very long-term memory in MS, the question of cognitive impairment in this domain remains a matter of debate. Please also refer to Table 2 for an overview of discussed procedures.

**Measures of Executive Function**

Executive functions refer to higher-order cognitive functions including reasoning, planning, inhibition, and flexibility. Their status in MS patients is less well assessed than that of the cognitive functions discussed in the previous sections, i.e., attention and memory (Benedict et al., 2002). Executive dysfunctions seem to appear somewhat less frequently than memory or IPS-deficits (Bobholz & Rao, 2003), though other authors pointed out that the majority of MS patients showed at least some kind of executive deficit (Drew et al., 2008). This seems to be especially prominent in chronic-progressive patients (Calabrese, 2006). In addition, there is a certain body of evidence showing that executive dysfunction in MS might be the result of depression and not of MS itself (Arnett, Higginson, & Randolph, 2001). Drew et al. (2008) pointed out that there is probably no “typical” profile of executive dysfunctions in MS. Nevertheless, their relevance in MS remains because they also negatively influence other cognitive domains (Beatty & Monson, 1996; Foong et al., 1997). Also, as DeSousa et al. (2002) stressed in their review, “abnormalities in abstract thinking and executive functions can be particularly disabling for patients whose jobs require high intellectual input.”

From a neurological viewpoint, executive deficits occur consequently in MS since executive tasks require the integrity of complex neural networks because of their complex cognitive demands (Hildebrandt, Brokate, Lanz, Ternes, & Timm, 2003). However, this integrity is often compromised because of white-matter lesions resulting in cortico-cortical disconnections (Hoffmann et al., 2007). Furthermore, in line with the observation that executive functions are usually associated with frontal lobe activity (Lezak, 2012), a recent review of imaging studies on MS...
patients concluded that most of the studies reported correlations between executive dysfunction and lesion load in frontal brain areas (Rocca et al., 2015).

Nonetheless, tests of executive function appear to be underrepresented both in cognitive screenings as well as extensive test batteries (Hansen et al., 2017; McNicholas & McGuigan, 2016).

An overview of presented procedures can be seen in Table 3.

### Table 3. Procedures for assessing executive functions.

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Cognitive Subfunction</th>
<th>Strengths and Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin Card Sorting Test (WCST)</td>
<td>Heaton et al. (1993)</td>
<td>Concept formation and reasoning</td>
<td>+ probably the most often employed test for executive function in MS + large amount of validation data in MS + supposedly differentiates between MS-subgroups – somewhat lengthy (up to 45 minutes)</td>
</tr>
<tr>
<td>Delis-Kaplan Executive Function Score (D-KEFS)</td>
<td>Delis et al. (2001)</td>
<td>Several aspects of executive function, assessed through nine subtests that may be employed separately</td>
<td>+ ideally suited for testing specific questions + some subtests include paradigms well researched in MS – insufficient validation of specific forms in MS</td>
</tr>
<tr>
<td>Standard Progressive Matrices (SPM)</td>
<td>Raven (1936)</td>
<td>Reasoning general cognitive ability</td>
<td>+ long history of employment in MS + differentiates well between patients and healthy controls – insufficient validation data in MS – missing correlation with other measures of executive function</td>
</tr>
<tr>
<td>Tower of Hanoi (ToH), Tower of London (ToL)</td>
<td>Goel &amp; Grafman (1995), Tucha &amp; Lange (2004)</td>
<td>planning and decision-making logical problem solving</td>
<td>+ some research exists in MS + patient groups tend to perform worse than controls – possibly confounded with psychomotor speed – when testing is untimed, patients’ performance is on par with controls</td>
</tr>
<tr>
<td>Regensburger Wortflüssigkeitstest (RWT); Controlled Oral Word Association Test (COWAT); Word List Generation (WLG)</td>
<td>Aschenbrenner et al. (2000); Benton &amp; Hamsher (1989); Rao et al. (1990)</td>
<td>verbal fluency language ability psychomotor speed semantic memory</td>
<td>+ well-documented deficits in MS patients + large body of clinical evidence points to the predictive value of fluency measures + short and easy to administer +/- performance relies on several factors</td>
</tr>
<tr>
<td>Five Point Test (FPT)</td>
<td>Regard et al. (1982)</td>
<td>nonverbal fluency psychomotor speed</td>
<td>+ short and easy to administer + norms for strategy use allow qualitative assessment – only limited study data available – confounding with motor disability</td>
</tr>
<tr>
<td>TAP subtests Flexibility, Go/NoGo, Shift of Attention, Working Memory</td>
<td>Zimmermann &amp; Fimm (2009)</td>
<td>several aspects of attentional processes and executive control</td>
<td>+ suitable for specific questions + some study data point to the validity of single subtests in MS – no systematic research on the validity of the TAP in MS – operationalization of constructs is questionable for some subtests</td>
</tr>
<tr>
<td>Stroop-Test</td>
<td>Bäuml (1985)</td>
<td>attention processing speed cognitive flexibility inhibition</td>
<td>+ large body of clinical studies available in MS + discriminates well between patients and controls + no confounding with motor dysfunction – possible confounding with visual impairments/visuospatial deficits – influence of psychomotor speed in interference condition is still unclear</td>
</tr>
<tr>
<td>Trail-Making Test (TMT)</td>
<td>Reitan (1955)</td>
<td>processing speed visuomotor tracking cognitive flexibility divided attention</td>
<td>– confounding with motor and visuospatial dysfunction as well as processing speed – does not discriminate well between patients and controls</td>
</tr>
</tbody>
</table>

#### Tests of Concept Formation and Reasoning

The Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Curtiss, Kay, & Talley, 1993) is probably the best-established test of executive function in MS. The patient sorts a set of stimulus cards according to a predefined rule. This rule is not revealed to the patients, but rather patients have to find it out on their own. Once patients have consecutively applied this rule, it is replaced by a new rule, and the
ties on the WCST are based on general conceptual impairments. A follow-up study (Beatty & Monson, 1996) compared performance on the WCST with performance on the California Card Sorting Test (CCST; Delis, Bihrle, Janowsky, Squire, & Shimamura, 1989). In many ways, CCST and WCST are comparable measures. However, as Beatty (1993) pointed out, some of the WCST scores might be confounded with memory functions – a problem supposedly avoided by employing the CCST. Results indicated that patients tended to be impaired on both tests. In the WCST, the profiles of MS patients resembled those of other patient groups with frontal lobe dysfunction, whereas in the CCST profiles of MS patients were distinct and mainly associated with concept formation. Nonetheless, the WCST has proven itself to be a valid – albeit somewhat lengthy – assessment tool for executive dysfunction in MS populations. Consequently, it continues to see regular use as a predictor of cognitive impairment in clinical studies (Mattioli et al., 2016b; Patti et al., 2015; Radomski et al., 2015), while hardly any further research regarding the CCST in a MS population has been attempted.

More recently, the Sorting subtest of the Delis-Kaplan Executive Function Score (D-KEFS, Delis, Kaplan, & Kramer, 2001) was proposed as a measure of executive function in an extensive test battery for MS patients (Benedict et al., 2002). The D-KEFS comprises nine tests assessing different aspects of executive function. The most part, these tests are modified versions of previously existing ex-

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**Table 3. Procedures for assessing executive functions. (continuation)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Cognitive Subfunction</th>
<th>Strengths and Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>Strauss et al. (2006)</td>
<td>working memory</td>
<td>+ differentiates well between cognitively impaired and preserved patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>divided attention</td>
<td>+ short</td>
</tr>
<tr>
<td></td>
<td></td>
<td>processing speed</td>
<td>+ no fine-motor functions required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ extensively researched in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ parallel forms exist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– possible confounding with mathematical ability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– still unclear which cognitive function constitutes the main aspect of PASAT performance</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>– stressful and demanding</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>– frequently rejected by patients</td>
</tr>
<tr>
<td>Testbatterie zur Aufmerksamkeitsprüfung (TAP), subtest Working Memory</td>
<td>Zimmermann &amp; Fimm (2009)</td>
<td>working memory</td>
<td>+ sufficient norms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>attention</td>
<td>– confounding factors are attention and psychomotor speed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– only limited study data in MS</td>
</tr>
<tr>
<td>Verbal and Nonverbal Digit Span (WMS) backwards</td>
<td>Härting (2000)</td>
<td>working memory</td>
<td>+ some validation data exist in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>attention</td>
<td>+ very basic and easily executed test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>short-term memory</td>
<td>– attention is a confounding factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– appears to differentiate only marginally between patients and controls</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale (WAIS)</td>
<td>Wechsler (2008)</td>
<td>working memory</td>
<td>+/- pros/cons basically comparable to Verbal Digit Span backwards, but less clinical data in MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>attention</td>
<td></td>
</tr>
</tbody>
</table>
cutive function tests, which have been slightly modified or which have been given new normative data. Each test is supposed to represent a standalone measure. In the Sorting subtest, which is based on the WCST, patients have to group a number of cards according to as many different concepts or rules as they can possibly think of. The test supposedly measures conceptual reasoning and permits the differentiation of concept formation from conceptual flexibility (De-lis et al., 2001). Thus, the paradigm is remotely related to that of the WCST but in fact might assess different aspects of reasoning and concept formation. An expert panel (Benedict et al., 2002) proposed parts of this test as a measure of executive function in the MACFIMS test battery. However, this panel failed to provide any study data to underline their decision. This was – at least in part – amended by Parmenter et al. (2007c), who compared the validity of both the WCST and the D-KEFS Sorting subtest in a MS population. They reported that both discriminated between patients and controls, but the Sorting subtest did so only after controlling for depression. The finding that executive dysfunction in MS might be confounded by depression was also acknowledged by Arnett et al. (2001). Furthermore, both correlated with MRI lesion burden, and both discriminated between employed and disabled patients. Parmenter et al. (2007c) concluded that, since the Sorting subtest offers alternative forms, it might at least be a valid alternative to the WCST for regular controls.

Another test that has been used regularly as a measure of reasoning ability in MS patients is the Standard Progressive Matrices (SPM), originally developed by Raven (1936). These consist of several matrices missing one element. The patient recognizes the underlying logic of each matrix in order to fill in the missing element (Strauss et al., 2006). Just like the WCST, results on the SPM significantly contributed to the prediction of cognitive test performance in MS patients in early systematic studies (Rao et al., 1989b), and results on the SPM also differentiated between MS patients and healthy controls (Rao et al., 1991). Just like the WCST, the SPM were recommended as part of an extensive test battery in MS (Peyser et al., 1990), and a review by Zakzanis (2000) reported that among all considered tests of executive function, the SPM were the most sensitive to differences between the MS group and controls. This finding is in line with results from a meta-analysis by Prakash et al. (2008), who found significantly greater impairment of MS patients in tests of nonverbal intelligence (including the SPM) in comparison to tests of verbal intelligence.

Nonetheless, in recent years, little to no use has been made of SPM or other matrices by Raven. This may be attributed to the fact that Foong et al. (1997) reported a missing relationship between the results of the Advanced Progressive Matrices (APM) and executive dysfunction as measured by other tests. It was concluded that APM is more of a measure of general intellectual functioning, which also is more in line with its original purpose to assess nonverbal intelligence (Strauss et al., 2006). This conclusion might also be extended to the SPM. Thus, it remains unclear what the Progressive Matrices exactly measure. Even though they still see regular use in several contemporary MS studies, they are not usually employed to assess executive functioning, but rather as an indicator of general cognitive ability (BrisGatt et al., 2013; Nocentini et al., 2014; Tinelli et al., 2013).

Finally, a couple of subtests of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 2008) supposedly assess verbal reasoning and have seen frequent use in MS studies: The comprehension subtest of the WAIS consists of questions concerning solutions to day-to-day problems as well as the applicability and understanding of social rules and abstract concepts. It has been reported that lower scores on this test are associated with disease progression (Filley, Heaton, Thompson, & Nelson, 1990) and are also significantly associated with MRI measurements of the corpus callosum (Rao, 1990b). It has also been proposed as part of a larger test battery for cognitive assessment in MS (Peyser et al., 1990). However, more recent studies did not find a significant difference in performance between MS patients and healthy controls on the comprehension subtest (Olivares et al., 2005), and a review study reported only small effects for all patients with MS in comparison to healthy controls (Zakzanis, 2000).

In the similarities subtest of the WAIS, patients are confronted with two words or concepts. The task is to describe in which way they are similar. A review by Zakzanis (2000) identified seven studies that employed this subtest for discriminating between MS patients and healthy controls. They concluded that it was only a mediocre predictor for discrimination purposes, with a discrimination rate of 30%. Nonetheless, the effects were much greater if only those patients with chronic-progressive MS were considered.

Another WAIS subtest – picture arrangement – supposedly assesses perceptual reasoning in MS. As the name implies, the patient arranges a number of pictures to achieve a meaningful order. Both Beatty and Monson (1994) as well as Filley et al. (1990) reported this subtest to be sensitive to diffuse neuronal damage because of MS. Beatty and Monson concluded that MS patients tend to exhibit a deficit in sequencing tasks which is at least partly dissociable from motor impairments.

Tests of Planning and Decision-Making

Only a limited number of studies have taken tests of planning, decision-making, and logical problem-solving into consideration when diagnosing cognitive deficits in MS patients. Among them, the so-called “tower tests” – i.e.,
Differentiate well between MS patients and healthy controls. Of the D-KEFS, implying that this procedure does not differentiate to assemble a cube out of a number of 27 smaller cubes. Link’s probe Metzler, 2000). The task requires the participant to assemble a cube out of a number of 27 smaller cubes. “Standardisierte Link’sche Probe” (SLP, Standardized Zettl, 2005) as a part of the diagnostic repertoire in MS, is problem solving, which was proposed (Engel, Greim & Zettl, 2005) as a part of the diagnostic repertoire in MS, is represented. Patients move a number of disks or beads from a starting position to a predefined goal position by moving as few moves as possible. Various versions of these tasks have abounded, and even on close inspection, some studies remain unspecific as to which one was employed. This might be considered somewhat encumbering concerning comparability. Overall, neuropsychological research has demonstrated that MS patients tend to perform poorly on these planning tasks, including the Tower of Hanoi (Arnett et al., 1997; Radomski et al., 2015), the Tower of London (Arnett et al., 2001; Denney, Sworowski, & Lynch, 2005; Foong et al., 1997) and the tower task included in the D-KEFS (Drew et al., 2008).

Both Arnett et al. (1997) and Foong et al. (1997) reported worse performance of MS patients in the Tower of London task. They solved significantly fewer problems than controls, and this effect grew more pronounced with increasing difficulty of the task (Foong et al., 1997). While Arnett et al. (1997) reported that differences between MS patients and controls were for the most part relatable to patients with chronic-progressive MS, Foong et al. (1997) reported a general impairment of MS patients on this task. On the other hand, Drew et al. (2008) found that 14% of their MS sample scored less than 1 SD below the mean on the tower subtest of the D-KEFS, implying that this procedure does not differentiate well between MS patients and healthy controls.

Arnett et al. (1997) reasoned that several factors such as working memory and psychomotor speed affected performance, and in a later study (Arnett et al., 2001) they amended that deficient planning ability is also associated with depression in MS. On the other hand, Foong et al. (1997) concluded that deficient performance of MS patients on the Tower of London is attributable to general cognitive decline, since they could not make out any specific lesions to frontal brain areas associated with these deficits. Furthermore, Drew et al. (2008) observed that physical disability seemed to be a confounding factor on the D-KEFS tower task.

A contemporary study by Owens, Denney, and Lynch (2013) quite successfully merged the previous findings: Interpreting results of their own MS patient sample, the authors concluded that deficiencies in planning ability in the Tower of London are evident only when time is restricted. Therefore, deficiencies on this task should be considered as a relative consequence of reduced information processing speed, which is a typical MS-related problem.

Another test of visuoconstructive planning ability and problem solving, which was proposed (Engel, Greim & Zettl, 2005) as a part of the diagnostic repertoire in MS, is the “Standardisierte Link’sche Probe” (SLP, Standardized Link’s probe Metzler, 2000). The task requires the participant to assemble a cube out of a number of 27 smaller cubes, observing that the coloring of the outer faces is uniform. A study by Schulz et al. (2006) employed the SLP among several other tests of cognitive function and reported a highly significant difference between patients and healthy controls. However, to our knowledge this was the only study to date that employed the SLP in this context.

A review of the currently available clinical evidence shows that it remains unclear whether tests of planning ability distinguish well between MS patients and healthy subjects. Furthermore, whether MS patients as a group show specific deficits in this cognitive domain remains at least questionable, since there may be confounding effects of psychomotor speed (Owens et al., 2013). Also, all of the above-mentioned tasks require a certain amount of visuospatial and visuoconstructive ability, which has also been reported to be frequently impaired in MS (see next section). On a final note, a comparison between nonverbal (based on visuospatial or visuoconstructive skills) and language-based planning abilities might help to further differentiate whether deficiencies in planning tasks are confounded with visuospatial abilities in MS patients. Language-based alternatives that come to mind for this purpose are tasklists as outlined by von Cramon & Matthes-von Cramon (1993). Such tasklists usually require the patient to solve a verbal planning task with a limited number of degrees of freedom, i.e., scheduling appointments or planning a day. However, to our knowledge no research concerning this question has been initiated to date.

Tests of Productivity

Tests of productivity—or fluency—“evaluate the spontaneous production of words under restricted search conditions” (Strauss et al., 2006). These restricted conditions may include categories (semantic fluency) or words beginning with a specific letter (phonemic fluency). In both conditions, the dependent variable is the number of words generated in a certain timeframe (usually 1–2 Minutes). Common tests are the Regensburger Wortflüssigkeitsat test (RWT, Regensburg word fluency test Aschenbrenner, Tucha, & Lange, 2000), Controlled Oral Word Association Test (COWAT, Benton, Hamsher, & Sivan, 1989), and Word List Generation Task (WLG, Rao, 1990a).

In MS patients, deficits on such verbal fluency measures have been well documented for quite some time (Pozzilli et al., 1991; Rao et al., 1989b). Over the past decades, a nearly overwhelming body of evidence has been amassed for a significant disease effect on verbal fluency measures (Batista et al., 2012; Brissart et al., 2013; Briken et al., 2014; Camp et al., 1999; Drew et al., 2008; Foong et al., 1997; Heesen et al., 2010; Hildebrandt et al., 2003; Huijgbregts et al., 2004; Kujala et al., 1997; Tröster et al., 1998). Henry and Beatty
(2006) also noted that MS patients showed substantial deficits in both phonemic and semantic fluency. This effect was so pronounced that it appeared in their meta-analysis as the most indicative neuropsychological measure for cognitive impairment. An assessment of verbal fluency is also part of the MACFIMS (Benedict et al., 2002) as a measure of deficient word retrieval. The authors acknowledge that verbal fluency measures rely on both the speed and efficiency of word retrieval from lexical memory. Therefore, they are in line with other “dirty” (Hoffmann et al., 2007) but highly predictive tests such as the PASAT or the SDMT.

Regarding the question whether a semantic or phonemic fluency measure is preferable, Beatty (2002) concluded that both have comparable predictive values.

Nonetheless, it should be noted that not all studies employing verbal fluency measures found significant disease effects. A study by Glanz et al. (2007) considered the performance of both newly diagnosed MS patients and patients with clinically isolated syndrome (CIS) and found that the patients were impaired in tasks such as the SDMT and PASAT, which would be expected in an MS population. However, their patients did not show impairment on a verbal fluency measure. Therefore, it might be deduced that verbal fluency measures are not as sensitive to cognitive decline as other established measures in this early phase of the disease.

Also, tests of fluency are known to be highly susceptible to depression (Beblo & Lautenbacher, 2006; Henry & Crawford, 2005). Since depression is a prevalent condition in MS, its possible influence on fluency measures should not be underestimated. Further research on this question in MS is certainly warranted.

On a final note, tests of nonverbal fluency such as the Ruff Figural Fluency Test (RFFT, Ruff, Light, & Evans, 1987) and the Five Point Test (FPT, Regard, Strauss, & Knapp, 1982) have been considered as a diagnostic tool for assessing fluency in MS as well (Boddon & Kalbe, 2010), but study data on this topic are scarce. Drew et al. (2008) reported that MS patients were comparably less impaired on the design-fluency task of the D-KEFS than on verbal-fluency measures. On the other hand, the results of a recent study by Hansen et al. (2017) suggest that the FPT might be a suitable measure for executive dysfunction in general when screening for cognitive impairment in MS. Yet confounding factors such as motor and visual impairment need to be taken into account when interpreting results of design fluency tests in MS.

### Tests of Flexibility, Shifting, and Inhibition

Cognitive flexibility, shifting, and inhibition may be summarized as self-regulatory processes. According to Lezak et al. (2012) “it may appear as inability to shift perceptual organization, train of thought, or ongoing behaviour to meet the varying needs of the moment.”

A prominent task in this context is the Stroop paradigm (i.e., Bäuml & Stroop, 1985). (Please refer to the “Tests of Attention” subsection for an explanation of the test concept.) The Stroop effect has long been regarded as a measure of frontal lobe dysfunction (Lezak et al., 2012), and first evidence that the Stroop Test (ST) might be an appropriate measure of cognitive decline in MS was reported by Rao et al. (1989b): The results of the ST correlated with total lesion area in their early MRI study. Consequently, Peyser et al. (1990) included the ST in their core battery of neuropsychological tests. Two meta-analyses revealed that the interference condition of the ST was a sensitive measure for deficits in cognitive flexibility and a good discriminator between MS patients and healthy controls (Prakash et al., 2008; Zakzanis, 2000). Drew et al. (2008) tested 97 MS patients on a wide range of executive function scores. They reported that most number of impairments on tasks of fluency, shifting, and inhibition such as the Stroop paradigm and the TMT-B. Furthermore, the color-word-inhibition task was the only one of these tests not significantly correlated to physical disability. Portaccio et al. (2010) employed the ST as an additional test for executive function in their longitudinal study testing the Brief Repeatable Battery (BRB). Several recent studies have also used the ST, for instance, as an outcome parameter for cognitive training in MS, with varying results (Amato et al., 2014; Cerasa et al., 2012; Chillemi et al., 2015).

Several additional studies have focused on Stroop performance in MS patients: Kujala, Fortin, Reuvenso, and Ruutiainen (1995) and Kujala et al. (1997) reported distinct differences between cognitively preserved and mildly deteriorated MS patients in both the naming and the interference condition of the ST, while cognitively preserved MS patients and controls did not differ on these parameters. They interpreted these results as a general consequence of cognitive processing slowness in the group of mildly deteriorated patients. Some other studies also attributed these impairments in large part to reduced processing speed (Denney & Lynch, 2009; Lynch et al., 2010; MacNiven et al., 2008), while others also highlight the role of executive functions in performing the ST. For instance, an MRI study by Pujol et al. (2001), consisting of a sample of 45 MS patients, revealed that both frontal and parietal lesions account for time variance in the interference task. Specifically, response times were pronouncedly prolonged in patients with more right frontal lesions, whereas the interference condition was specifically impaired in patients with lesions predominantly in the left posterior parietal region. This might be interpreted as support for the notion that several cognitive functions are tapped by the ST.
A recent approach to impairment on the ST in MS patients centered on event-related potentials (Amato et al., 2016). The study involved two groups of MS patients (“frontal” – scoring low on tests of executive function, and “non-frontal” – scoring average on such tests), as well as a healthy control group. Abnormally decreased activity was found in the group of “frontal” MS patients over the frontal, cingulate, and parietal regions in the N1, N2, P3, and N4 windows. The authors concluded that cognitive impairments as measured by the ST are correlated with decreased bioelectrical activity relatable to executive dysfunctions regarding selective attention, response inhibition, and conflict monitoring.

In summary, it remains unclear whether the ST is more a measure of information processing speed or of executive function; it probably could be considered as falling in both categories, but its predictive value in discerning cognitive dysfunctions in MS has been proven in several studies. Nonetheless, caution in the interpretation of these studies is warranted since – as Strauss et al. (2006) pointed out – several different versions of the ST are in circulation, making comparability questionable.

Another test of shifting and cognitive flexibility is the Trail Making Test-B (TMT-B, Reitan et al., 1971). This test was also introduced in the “attention” subsection, and its rationale is explained there. While the TMT-B – like TMT-A – relies on psychomotor speed, it also involves shifting and mental flexibility since participants alternate between numbers and letters as target stimuli. Generally, there appears to be a close relationship between TMT-B results and the results of other tests of executive function such as the WCST (Libon et al., 1994; Ricker, Axelrod, & Houtler, 1996). A study by Stuss et al. (2001) reported notable slowing on the TMT for patients with frontal lobe damage. However, the best predictor for frontal lobe lesions were the number of errors in the TMT-B. However, in their meta-analysis, Zakzanis (2000) pointed out that of all considered tests of cognitive flexibility, the TMT-B was the worst discriminator between MS patients and controls. Furthermore, it cannot be ruled out that bad performance of MS patients on the TMT-B is associated with impaired motor abilities (Drew et al., 2008). Nonetheless, the TMT-B continues to be employed as a clinical outcome measure (i.e., Cerasa et al., 2012). In their study sample of 29 MS patients, Chillemi et al. (2015) reported that patients were significantly slower on the TMT-B than controls. However, if we put the results of TMT-B into perspective by comparing them with the results of TMT-A, which has been proposed as a more appropriate measure of cognitive flexibility (Kourtidou, Kasselimis, Potagas, Zalonis, & Evdokimidis, 2015; Sánchez-Cubillo et al., 2009), no significant slowing was found in the patient group. This result further questions the usefulness of the TMT-B as a measure of executive function in MS, though further research on this subject is certainly warranted.

Finally, several computerized tests exist that measure shifting, inhibition, and cognitive flexibility under timed conditions. For that purpose, several subtests of the TAP (Zimmermann & Fimm, 2009) were employed either as outcome measures or as comparative parameters in MS-related studies, among them “shift of attention” (Briken et al., 2014; Heesen et al., 2010), “go–nogo” (Hansen et al., 2015; Pöttgen et al., 2015a; Schulz et al., 2006) and “flexibility” (Fischer et al., 2014; Kunkel et al., 2015; Schulz et al., 2006). All of these studies found significant effects of disease on the mentioned parameters, making them potentially relevant for diagnosing cognitive deficits in MS. However, the validity of these tasks in an MS population must be considered at least questionable, since there is only a very limited body of research concerning confounding factors such as information processing speed. For instance, a comprehensive study by De Sonneville et al. (2002) analyzed the performance of 53 MS patients versus 58 controls on a large set of various computerized tests of attention, response organization, and flexibility. They reported that, overall, MS patients were 40% slower than controls, irrespective of the task. They also scored worse on accuracy parameters. On the other hand, the authors also reported a further increase in reaction times on those tasks that include executive components. It is reasonable to assume that this additional increase cannot be explained by mere motor slowing or information-processing speed deficits, but that task-specific executive demands contribute to a further slowing.

### Tests of Working Memory

The term “working memory” describes memory processes that are used to plan and carry out behavior (Galanter & Pribram, 1960). Therefore, there is a considerable overlap with memory functions. Nonetheless, working memory should be viewed as a compound cognitive function that also requires attentional and processing reserves (Cowan, 2008). Its categorization as an executive function is reflected in the three-component model of working memory by Baddeley (2000), where a “central executive” manipulates information from visual and phonological buffers by controlling attention-related processes. While it has been a matter of debate whether difficulties in working memory tasks in MS stem from problems associated with these buffers (e.g., Litvan et al., 1988) or the central executive (e.g., D’Esposito et al., 1996), deficient processing speed also appears to be a confounding factor (Lengenfelder et al., 2006; Lynch et al., 2010). Consequently, there is a certain amount of redundancy when reviewing tests of working memory, since some also qualify as tests of attention, while others might also be interpreted as tests of memory.
Even though this redundancy might be detrimental to a test’s interpretation as regards its specificity, it has been argued that the predictive value of such “dirty tests” in diagnosing the overall cognitive impairment in MS is especially high (Hoffmann et al., 2007). One reason for this might be that diffuse damage to cortico-cortical connections is far more frequent than heavy lesion load in specific cortical regions. Therefore, patients tend to be more frequently impaired on tasks requiring widely spread cortical networks and greater intercortical connection.

The TAP subtest “working memory” (Zimmermann & Fimm, 2009) consists of a computerized, visually presented N-back task. According to the authors, the test assesses attentional control and updating of continuously presented information and should therefore be considered as a working memory paradigm. As previously discussed, the TAP has seen only infrequent application in MS diagnosis. Also, motor deficits must be taken into account when interpreting results of TAP subtests, which are designed as reaction time tasks. Nonetheless, some studies point toward the usefulness of this visual N-back paradigm in diagnosing working memory deficits in MS. Penner et al. (2001) reported reduced frontal and precuneal cortical activity during the TAP subtest “working memory” in an fMRI study in patients with MS and healthy controls. In the same study, the allegedly simpler attentional task “TAP – alertness” was marked by heightened activity in several cortical regions in MS patients in comparison to controls. The authors concluded that MS patients could – at least partially – compensate for deficits on simple reaction time tasks by showing greater effort than controls. However, greater effort could no longer compensate for cognitive deficits in more complex cognitive functions such as working memory. Schulz et al. (2006) reported significantly slower processing on this task compared to healthy controls, although this result might have been confounded with the demands to psychomotor speed inherent in this paradigm. Concerning its application in contemporary studies, the working memory subtest of the TAP has also seen occasional use as an outcome parameter evaluating the effects of cognitive training in MS (Vogt et al., 2009).

A simple measure for assessing working memory is digit span backwards, which is realized on the Wechsler Memory Scale (WMS; Härting et al., 2000) as well as on the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2008). The WMS also includes a nonverbal variant of this test (block-tapping; see also the “Corsi block-tapping task” (Kessels et al., 2000). Analogous to digit span forwards, the patient repeats the presented string of digits in backwards order. Additionally, the WAIS includes a related but somewhat more complicated paradigm: The patient orders a verbally presented string of letters and numbers by repeating first the numbers and then the letters, both in ascending order (WAIS – Letter Number Sequencing). Since these measures are easily obtained and take up little time, they have been employed regularly in diagnosing cognitive function in MS (Ivnik, 1978; Rao et al., 1989a; Rao et al., 1991) and still see frequent use (La-margue–Hamel et al., 2015; Pöttgen et al., 2015a; Schulz et al., 2006; Vogt et al., 2009). Rao et al. (1989a) reported significant differences between MS patients and healthy controls on the digit span backwards task of the WAIS. In contrast, digit span forward is usually reported to be unaffected in MS (Calabrese, 2006). Even though these tests have an unquestionable component of working memory, it has been pointed out that results are often confounded with attentional deficits in MS (Beatty, 1995b). Also, in a study by DeLuca, Chelune, Tulszy, Lengenfelder, and Chiara-valloti (2004) employing the WAIS – Letter Number Sequencing subtest, the authors reported that only a small amount of severely impaired patients showed any deficits on this task. However, a significantly larger part of their sample showed impairment on the PASAT. They concluded that the main deficit in information processing in MS is speed of processing, and not working memory. On a final note, a meta-analysis by Zakzanis (2000) concluded that, although digit span backwards is one of the most commonly employed measurements in diagnosing cognitive deficits in MS, it differentiated only marginally between patients and healthy controls.

Finally, the Paced Auditory Serial Addition Test (PA-SAT) is also both a test of attentional processing as well as working memory. (See above for a closer description of the test and its widespread application in MS.) As was already pointed out, the Paced Auditory Serial Addition Test (PA-SAT) is considered to be one of the most indicative tests when determining cognitive status in MS (e.g., Langdon, 2010), and most researchers acknowledge the role of working memory for completing the task (e.g., Benedict et al., 2002; Brittain, La Marche, Reeder, Roth, & Boll, 1991; Hansen et al., 2017). Several MRI studies reported abnormal findings for MS patients in cortical regions associated with working memory when performing classical N-back tasks (Cader, Cifelli, Abu-Omar, Palace & Matthews, 2006; Duong et al., 2005; Vacchi et al., 2017). While cognitively preserved patients tend to respond to such tasks with a hyperactivation (comparable to healthy controls) of associated cortical areas (especially in the superior frontal and anterior cingulate gyrus) which may limit clinical expression of the disease, frontal hyperactivation is lost over the course of the disease. These findings point to an adaptive mechanism in the working memory network. On the other hand, results of most contemporary studies employing the PASAT suggest that the problems many MS patients experience while performing the PASAT are mainly dependent on information processing speed (DeLuca et
al., 2004; Genova, Lengenfelder, Chiaravalloti, Moore, & DeLuca, 2012). This is not necessarily a contradiction, since reduced processing speed may be compensated for by higher activation of working memory networks on such tasks as the PASAT – but only up to a certain degree of cortical lesion load (Vacchi et al., 2017). Therefore, it might be more appropriate to employ tests which minimize requirements to information processing speed when explicitly testing for working memory deficits in MS.

See Table 3 for an overview of diagnostic procedures discussed in this section.

**Tests of Visuospatial Perception**

Besides basic cognitive functions like attention, memory, and executive control, MS patients also appear to be frequently impaired in their visuospatial skills, although there has only been little work regarding this matter. Rao et al. (1991) were amongst the first to report that visuospatial perception was more commonly impaired in MS patients than previously estimated. Even though this conclusion has been questioned in recent years (e.g., Calabrese, 2006), Fisher et al. (2001) concluded that the prevalence rates for impairments of visuoperception were among 12 to 19 percent. Vleugels et al. (2000) reported even higher prevalence rates. Considering that many MS patients experience initial symptoms associated with an inflammation of the optic nerve, high prevalence rates of visual impairment are a logical consequence. Furthermore, since all visuospatial skills rely on visual perception, deficits in tests of visuospatial functions might well be confounded with impaired visual perception. Indeed, up to 75% of MS patients experience optic neuritis as an initial symptom or during the course of the disease (Kaur & Bennett, 2007). Further evidence points to the fact that visual deficits from optic neuritis regularly persist in a significant number of patients (Jasse et al., 2013). Even though this finding helps to explain the reported high prevalence rates of visuospatial impairments, there may be cases where the reported deficits could not be solely accounted for by optic neuritis (Moreno, García, Marasescu, González, & Benito, 2013). Furthermore, since many of the neuropsychological measures introduced in the previous chapters rely on intact visuospatial perception, it is worthwhile to consider a defect in this system as a possible confounding factor for deficient test performance.

Therefore, Peyser et al. (1990) suggested including the Hooper Visual Organization Test (Hooper, 1983) as well as a modified version of the Block-Design Test (Wechsler, 2008) in routine neuropsychological examinations of MS patients. Both are used to assess visuospatial abilities. In the Hooper Test, participants have to recognize and name objects that have been cut into pieces and illogically arranged, while the block-design test requires rearrangement of variously colored blocks to match a certain pattern.

This set of tests was expanded by Rao et al. (1989b) and Rao et al. (1991), who included the Facial Recognition Test (FRT: Benton, 1994), Visual Form Discrimination Test (VFD, Benton, 1994), and Judgment of Line Orientation Test (JLO: Benton, 1994) in their neuropsychological battery. All of these tests assess certain aspects of visuoperception, including complex visual discrimination, prosopagnosia, and orientation. Both the FRT and the VFD at that time had already been described as discriminating between MS patients and controls (Beatty et al., 1988; Beatty et al., 1989; van den Burg et al., 1987).

The findings of Rao’s group on visuoperceptual impairments in MS were somewhat contradictory: Though they reported significant correlations between lesion load and performance in the Hooper Test (Rao et al, 1989b), no significant differences between MS patients and controls occurred (Rao et al., 1991). However, patients scored significantly worse than controls on the FRT, VFD, and JLO. In sum, these findings were interpreted as further evidence that visuospatial perception is frequently impaired in MS.

Some studies provided data supporting this finding (Pelosi, Geesken, Holly, Hayward & Blumhardt, 1997; Ryan, Clark, Klonoff, Li, & Paty, 1996; Vleugels et al., 2000). Other studies widened the scope of tests employable in this context: Schulz et al. (2006) reported that patients scored significantly worse than controls on the copy-trial of the Rey Complex Figure Test (Rey, 1941; see above). Both Bodden and Kalbe (2010) and Chillemi et al. (2015) consider the copy trial of the Rey Figure Test to be indicative of visuospatial organization deficits in MS. An interesting study by Moreno et al. (2013) included three case reports of MS patients with severe difficulties in the visual perception of objects and space, construction of figures under visual guidance, integration of figures into a whole, mental rotation of figures and elements, as well as using three-dimensionality. The authors concluded that these deficits could not be explained solely by visual impairment but had to be attributed to apperceptive visual agnosia, spatial agnosia, and constructional apraxia. The diagnosis of these deficits was conducted with the Visual Object and Space Perception Battery (VOSP, Warrington & James, 1991). Of all tests employed to diagnose dysfunctions in visuospatial perception, the VOSP is certainly the most comprehensive and versatile. It includes four subtests each for object and space perception. It should be mentioned, however, that the patients described in the case report study by Moreno et al. (2013) made up only a very small percentage of all patients considered for the study, and that their extensive deficits are observed only a very small percentage of all patients considered for the study, and that their extensive deficits are
certainly atypical for MS. Furthermore, MRIs of all patients included in this study showed a high lesion load with confluence periventricular lesions as well as additional lesions throughout the cortex, especially in parietal and occipital white matter regions.

A more recent study by Olivares et al. (2005) did not replicate the findings by Rao et al. (1991) concerning impairments in the JLO and FRT. Also, they did not find any significant differences between patients and controls on the Hooper Test and the Modified Block Design Test. Interpretation of these results is somewhat restricted since only a relatively small number (N = 33) of patients with initial relapsing-remitting MS (RRMS) were included. Nonetheless, this subgroup of patients did show a deficit profile characteristic of MS in measures of psychomotor speed and memory. Therefore, the lack of impairment in measures of visuospatial perception points toward the conclusion that such defects are unlikely in MS.

The most compelling argument against the assumption of a noteworthy impairment of visuospatial perception in MS comes from a meta-analysis by Zakzanis (2000) who considered six studies comparing patients and controls on up to nine measures of visuospatial perception and found that effect sizes were negligible for all employed procedures, though somewhat more pronounced for patients with chronic-progressive MS.

In summary, evidence concerning possible deficits in visuospatial perception in MS is somewhat weak. More recent research points toward the conclusion that visuospatial perception itself is affected only very infrequently. In most cases, deficits in tasks of visuospatial perception are likely attributable to either cognitive or motor slowing, or impairments in visual perception because of optic neuritis (Jasse et al., 2013; Zakzanis, 2000).

Nonetheless, an expert panel recommended including the JLO as an orienting procedure when extensively testing for cognitive decline in MS patients (Benedict et al., 2002).

### Summary and Recommendations for Neuropsychological Testing

Even though the problem of cognitive deficits in MS was recognized only late in comparison to other neurological dysfunctions, the past 20 years have seen a great effort on the part of neuropsychological researchers to fill this gap. Consequently, much research has been published concerning the diagnosis of cognitive deficits in MS, and several diagnostic procedures have been considered in this process. On the other hand, it should not go unmentioned that much less research has been published on the efficiency of neuropsychological therapy in MS, and many questions still remain even in the field of diagnostic approaches.

During the early beginnings of neuropsychological research in MS, authors concentrated on findings suggesting specific patterns of cognitive disabilities. With the advent of MRIs, comparisons of cognitive deficit profiles and cortical lesion load came to be investigated. At about the same time, validation of procedures and the establishment of standardized test batteries made up an important part of MS related cognitive research. Because of economic considerations, a main aspect of contemporary research has focused on shortening the employed testing procedures. This has led to the establishment of several screening procedures and their subsequent validation. The most prominent are a shortened version of the Brief Repeatable Battery (BRB, Rao, 1990a) and the Brief International Cognitive Assessment for MS (BICAMS, Langdon et al., 2012), both of which consist of two subtests focusing on information processing speed and verbal memory (BRB: SDMT and SRT; BICAMS: SDMT and CVLT). The short form of the BRB also includes the PASAT as a measure of executive function, while the BICAMS also assesses nonverbal memory and visuospatial ability via the BVMT. Both screening procedures have proven to be valid diagnostic instruments in the context of MS. Their usefulness derive not only from the fact that they try to span the width of possible neuropsychological impairments in MS. They also heavily rely on “dirty” tests of cognition, requiring intact cortico-cortical connectivity for good performance – a feature often found to be deficient in MS (Hoffman et al., 2007).

No compelling argument exists that would make one of them appear overwhelmingly superior over the other; rather, they should be employed as case-finding tools. This means that the decision whether an extensive neuropsychological diagnostic should be conducted is made contingent on the results of such a screening. Since screening procedures should produce a high sensitivity, a liberal threshold of one standard deviation (SD) below the mean should be applied when determining cognitive impairment. The Multiple Sclerosis-Neuropsychological Questionnaire (MSNQ), an instrument developed and validated by Benedict et al. (2003), might fulfill such a purpose, but this requires the presence of an informant, which is often not feasible. The MSNQ includes two questionnaires – a self-report- and an observer-rating. However, it has been shown that only informant data correlates satisfactorily with the neuropsychological status of the patient (Penner & Calabrese, 2007).

Following a conspicuous screening result, an extensive neuropsychological testing should ensue. Because of the variability of symptoms in MS, it is difficult to define a procedure that addresses all possible deficits exhaustively. Nonetheless, it is possible to construct a test battery that is...
best suited to assess those deficits most commonly found in MS. Such a test battery could then be adapted according to specific diagnostic questions such as vocational reintegration, exhaustibility, fitness to drive, or performance in specific cognitive domains. Several attempts have been made to construct such an extensive test battery (Franklin et al., 1988; Peyser et al., 1990; Rao et al., 1991).

The latest of these attempts is the Minimal Assessment of Cognitive Function in MS (MACFIMS, Benedict et al., 2002), which includes seven subtests encompassing five cognitive domains (see Table 4). In our opinion, MACFIMS constitutes a reasonable approach to neuropsychological assessment in MS, covering all discussed cognitive domains. Some adaptations might be sensible, as discussed throughout this section.

The first domain – processing speed/working memory – is covered both by the PASAT and the SDMT. According to our review, both tests certainly have proven to be prognostically valid in MS. The SDMT appears to slightly outweigh the PASAT concerning functionality. However, since the SDMT or possibly even both tests are already included in screening procedures, additional testing in an extensive battery would be redundant. Instead, we propose a basic assessment of attentional functions via a computerized procedure that covers both aspects of intensity and selectivity (see Figure 1). The combination of the TAP subtests Alertness, Go-NoGo, and Divided Attention has been discussed throughout this section.

The second domain assessed in the MACFIMS is learning and memory, which is covered by the CVLT and BVMT. It is certainly sensible to assess both verbal and nonverbal memory functions. Should the CVLT not be available, replacing it with a VLMT should not drastically reduce the prognostic validity of the testing. However, as mentioned in the corresponding section, the SRT and the CVLT should not be considered interchangeable. Therefore, even though the BRB already includes the SRT, additional testing with the CVLT in the extensive procedure is certainly reasonable. In return, since the BICAMS already includes the CVLT, additional testing with the SRT in an extensive procedure is also appropriate. Further in-depth testing of verbal memory functions might include story recall such as with the WMS subtest Logical Memory or even – probably very rarely – tests of very long-term memory. The BVMT should be included in the extensive procedure in any case. Should the BVMT not be available, a replacement with the Spatial Recall Test (7/24 or 10/36) or the ROCF is possible, but should be considered as the second best option (see Figure 1).

The third domain in MACFIMS is executive functions, which is covered by the Sorting subtest of the D-KEFS. It has already been pointed out that there is only limited evidence for the validity of the Sorting subtest in an MS population. However, because of its brevity and the presence of alternate forms, it might be favored over the WCST. If time is a factor, the WCST should still be favored over the Sorting subtest, since there is a large amount of study data pertaining to its applicability in MS.

Again, it should be noted that executive functions are frequently impaired in MS. Some contemporary authors consider deficits in executive functions to be as common as those in other cognitive domains (Calabrese 2006; Drew et al., 2008), and they may have a profound impact on daily life activities. Thus, we endorse a closer look on executive function in routine neuropsychological testing (see Figure 1). This is partly accomplished by including the PASAT in the screening, but other subcategories of executive function should also be included depending on the specific diagnostic question. For instance, tests of productivity (or fluency) are easily executed and should include the FPT for nonverbal productivity and the RWT for verbal productivity. Both rely heavily on information processing speed, which also makes them valuable as screening procedures, for instance, as a replacement for the PASAT. Tests of planning might include Tower tests, but also verbal planning tasks such as the Burgauer kleiner Planungstest (B-kPT, Burgau planning test Peschke, 2004). Finally, tests of shifting and flexibility such as the Stroop Test have also proven to be prognostically valid in MS.

The fourth domain covered in the MACFIMS is visual perception and spatial processing. In the corresponding section (see above), we concluded that no final decision can be made on the relevance for this domain in MS patients. Thus, a short procedure to assess these abilities is certainly appropriate. Here, the JLO is included. If additio-
nal testing is required, we advise using the VOSP, since it covers a wide range of possible defects in object and space perception (see Figure 1).

Finally, MACFIMS also covers the language domain via the COWAT, which is comparable to the RWT. Though spoken language is rarely affected in MS, we endorse the use of tests of verbal fluency in MS as a measure of executive control.

Additionally, questionnaires assessing depression and fatigue should be filled out by the patient regularly to control for confounding factors of mood and MS induced exhaustion. Concerning depression, a screening-questionnaire such as the Allgemeine Depressionsskala (ADS, depression scale Hautzinger, Bailer, Hofmeister & Keller, 2012) is generally preferable to the Beck-Depressionsinventar (BDI2, Beck depression inventory Beck, Steer, & Brown, 1996). This is largely because the BDI2 also covers bodily functions that are frequently impaired because of the disease.

When assessing fatigue, it is essential to employ questionnaires that differentiate between somatic and cognitive fatigue. Examples include the Würzburger Erschöpfungs-inventar für Multiple Sclerosis (WEIMUS, fatigue inventory for Multiple Sclerosis Würzburg Flachenecker, 2008) and the Fatigue Scale for Motor and Cognitive Functions (FSGM, Penner et al., 2009).

Finally, deficient motor control often constitutes a confounding factor when testing MS patients. In certain cases, it might be necessary to control for fine-motor functions. Appropriate tests in this context include pegboard tasks such as the Nine-hole peg test (Goodkin, Heertsgard, & Seminary, 1988). This is also part of the Multiple Sclerosis Functional Composite (MSFC, Fischer et al., 1999).

In summary, a wide array of neuropsychological testing procedures has been used in MS over the past decades. Their applicability is often questionable, but some procedures have proved to be diagnostically valid. Though some are not covered in this article, the most common and most comprehensively investigated are listed in their respective sections. Knowledge of these procedures and their pertaining study data in MS allows for the construction and adaptation of standardized test batteries. An example for such a neuropsychological assessment approach that relies on the conclusion drawn in this article can be seen in Figure 1. In clinical routine, these test batteries are supposed to serve several purposes: The first is to differentiate between cognitively impaired and preserved patients. The second is to assess the scope of cognitive deficits in MS and to provide a description of a cognitive profile. Based on this profile, conclusions concerning the necessity and form of neuropsychological therapy can be drawn. Early and reliable information on their cognitive status is also an asset for patients in order to help them make an informed decision concerning specific questions such as treatment options, vocational status, or fitness to drive. Finally, comparing baseline results of the neuropsychological testing with follow-up results provide valuable information about disease progress and treatment efficacy. The most recent and most promising of these test batteries, MACFIMS, has been analyzed according to information gathered in this article. Though we basically agree with its construction, we suggested some modifications and possible adaptations (see Figure 1). These modifications mainly concern tests of attention and information processing speed. We also provided some suggestions to further the scope of such a standardized test battery in order to investigate specific questions.

**Table 1.** Proposed adapted rationale for neuropsychological assessment.

*either SRT or CVLT, whichever did not occur in the screening.

**only if PASAT was not already executed during the screening.
References


<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>BICAMS</td>
<td>Brief International Cognitive Assessment for Multiple Sclerosis</td>
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<tr>
<td>B-kPT</td>
<td>Burgauer kleiner Planungstest</td>
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<td>BRB</td>
<td>Brief Repeatable Battery</td>
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<td>BTA</td>
<td>Brief Test of Attention</td>
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<td>BVMST</td>
<td>Brief Visuospatial Memory Test – Revised</td>
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<td>CCST</td>
<td>California Card Sorting Test</td>
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<tr>
<td>CIS</td>
<td>Clinically Isolated Syndrome</td>
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<td>CLTR</td>
<td>consistent long-term retrieval</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>COWAT</td>
<td>Controlled Oral Word Association Test</td>
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<td>CPMS</td>
<td>Chronic-progressive Multiple Sclerosis</td>
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<td>CVLT</td>
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<td>D-KEFS</td>
<td>Delis-Kaplan Executive Function Score</td>
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<td>Expanded Disability Status Scale</td>
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<td>FRT</td>
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<td>IPS</td>
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<td>ISI</td>
<td>interstimulus-interval</td>
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<td>JLO</td>
<td>Judgment of Line Orientation Test</td>
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<td>LTS</td>
<td>long-term storage</td>
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<td>MACFIMS</td>
<td>Minimal Assessment of Cognitive Function in Multiple Sclerosis</td>
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<tr>
<td>(f)MRI</td>
<td>(functional) magnetic resonance imaging</td>
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<td>FSMC</td>
<td>Fatigue Scale for Motor and Cognitive Functions</td>
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<td>Multiple Sclerosis Neuropsychological Questionnaire</td>
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<td>NSB</td>
<td>Neuropsychological Screening Battery</td>
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<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
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<td>PVSAT</td>
<td>Paced Visual Serial Addition Test</td>
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<td>PPMS</td>
<td>Primary progressive Multiple Sclerosis</td>
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<td>RFFT</td>
<td>Ruff Figural Fluency Test</td>
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<td>ROCF</td>
<td>Rey-Osterrieth Complex Figure Test</td>
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<td>RWT</td>
<td>Regensburg Wortflußigkeitstest</td>
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<td>SLP</td>
<td>Standardisierte Link’sche Probe</td>
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<td>Testbatterie zur Aufmerksamkeitsprüfung</td>
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<td>Verbal Learning and Memory Test</td>
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<td>VOSP</td>
<td>Visual Object and Space Perception Battery</td>
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<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
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<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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<td>WEIMUS</td>
<td>Würzburger Erschöpfungsinventar für Multiple Sclerosis</td>
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<td>WLG</td>
<td>Word List Generation Task</td>
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<td>WMS</td>
<td>Wechsler Memory Scale</td>
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1. Question: How common are cognitive deficits in multiple sclerosis according to the extant literature?
   a. They appear in merely a handful of patients.
   b. Approximately 10–20% of patients can be considered as having cognitive deficits.
   c. Approximately 20–30% of patients suffer from neuropsychological impairment.
   d. Approximately a good half of all MS-patients exhibit some more or less subtle cognitive deficits.
   e. The overwhelming majority of MS-patients tends to show cognitive impairments in some form.

2. Question: Which of the following cognitive domains is usually considered unaffected in multiple sclerosis?
   a. Attention and information processing speed
   b. Verbal memory
   c. General intelligence
   d. Executive functions
   e. Nonverbal memory

3. Question: Cognitive performance in multiple sclerosis may be confounded by a number of factors. Which one is not among them?
   a. Depression
   b. Cognitive fatigue
   c. Disease subtype
   d. Disease duration
   e. Physical disability

4. Question: A sensible and economical approach to neuropsychological assessment in multiple sclerosis should consist of the following steps:
   a. Run a screening for cognitive deficits. No further action is necessary since screenings differentiate sufficiently between cognitively impaired and preserved patients.
   b. Run a screening for cognitive deficits and in case of a conspicuous result, follow up with an extensive neuropsychological test battery.
   c. Each MS-patient should be tested extensively. Cognitive screenings are generally unsuitable in MS.
   d. Test each MS-patient extensively. In case of a conspicuous result, also run a cognitive screening.
   e. None of the above.

5. Question: The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a cognitive screening which assesses – among other functions – verbal memory. However, the developers of the BICAMS abstained from including a delayed memory trial in their screening. Which of the following options provides a sound methodological explanation for this approach?
   a. Verbal memory is only infrequently affected in MS and should thus not be overrepresented in a screening.
   b. Other than in e.g. Alzheimer’s dementia, MS-patients don’t usually suffer from significant information loss during retention intervals.
   c. The BICAMS already includes a subtest for delayed recall in nonverbal memory, making a parameter for delayed recall in verbal memory superfluous.
   d. In order to keep the screening short, the developers of the BICAMS decided to forego this parameter.
   e. The BICAMS is an unsuitable instrument for cognitive screening in MS and should therefore be avoided.
Um Ihr CME-Zertifikat zu erhalten (min. 3 richtige Antworten), schicken Sie bitte den ausgefüllten Fragebogen mit einem frankierten Rückumschlag bis zum 12.10.2017 an die nebenstehende Adresse. Später eintreffende Antworten können nicht mehr berücksichtigt werden.

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Die Ärztekammer Niedersachsen erkennt hiermit 1 Fortbildungspunkte an.

![Stempel]

**Neuropsychological Assessment in Multiple Sclerosis**

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Ich versichere, alle Fragen ohne fremde Hilfe beantwortet zu haben.

Name __________________________

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