Erfassung kognitiver Leistungsfähigkeit bei Patienten mit Multipler Sklerose

Inaugural-Dissertation

in der Fakultät Humanwissenschaften

der Otto-Friedrich-Universität Bamberg

vorgelegt von

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Bamberg, den 18.04.2018

Tag der mündlichen Prüfung: 19.11.2018

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URN: urn:nbn:de:bvb:473-opus4-537311
DOI: https://doi.org/10.20378/irbo-53731

Danksagung

Zuallererst gilt mein Dank meinem Doktorvater Professor Stefan Lautenbacher für seine andauernde wissenschaftliche und methodische Unterstützung bei der Dissertation.

Weiterhin gilt mein Dank Professor Patrick Oschmann für die Möglichkeit, an der Klinik für Neurologie des Klinikums Bayreuth GmbH im Rahmen der Forschungsabteilung zu promovieren.

Herrn Dr. Philipp Keune danke ich nicht nur für die fachliche Anleitung und Beratung bei der wissenschaftlichen Tätigkeit, sondern auch für die hervorragende zwischenmenschliche Zusammenarbeit.

Frau Jana Münßinger und Frau Simona Kronhofmann danke ich für ihre Hilfe bei der Datenerhebung, sowie ihre fortwährende motivationale Unterstützung.

Allen an dieser Dissertation beteiligten Patienten sowie allen weiteren beteiligten Mitarbeitern der Klinik für Neurologie danke ich für die gute und zahlreiche Unterstützung sowie für die konstruktive und angenehme Zusammenarbeit.

Ich danke meiner Großmutter Gisela Hansen dafür, dass sie mich die Bedeutung preußischer Tugenden lehrte, und meiner Mutter Silke Hansen dafür, dass sie nie müde wurde, meinen Horizont zu erweitern.

Meiner Frau Anna Hansen danke ich für ihre Kraft, Zuversicht und Liebe.

Widmung

Für Julius

Inhaltsverzeichnis

Abkürzungsverzeichnis

BICAMS	Brief International Cognitive Assessment for MS
BRB	Brief Repeatable Battery
BVMT	Brief Visuospatial Memory Test
CIS	clinically isolated syndrome - Klinisch isoliertes Syndrom
CLTR	consistent long-term retrieval
CVLT	California Verbal Learning Test
EDSS	Expanded Disability Status Scale
FPT	Fünf-Punkt Test
JLO	Judgment of Line Orientation Test
LTS	long-term storage
MACFIMS	Minimal Assessment of Cognitive Funtion in MS
MRT	Magnetresonanztomographie
MS	Multiple Sklerose
MSFC	Multiple Sclerosis Functional Composite
PASAT	Paced Auditory Serial Addition Test
PPMS	primary progressive multiple sclerosis - primär progrediente MS
RRMS	relapsing-remitting multiple sclerosis - schubförmig remittierende MS
RWT	Regensburger Wortflüssigkeits-Test
SD	standard deviation - Standardabweichung
SDMT	Symbol Digit Modalities Test
SLP	Standardisierte Link'sche Probe
SPMS	secondary-progressive multiple sclerosis - sekundär progrediente MS
SRT	Selective Reminding Test
TAP	Testbatterie zur Aufmerksamkeitsprüfung
VOSP	Visual Object and Space Perception Battery
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WLG	Word List Generation
WMS	Wechsler Memory Scale
ZNS	Zentrales Nervensystem

1.Einleitung

Multiple Sklerose (MS) ist eine chronisch entzündliche Erkrankung des zentralen Nervensystems (ZNS), welche mit einer Vielzahl neurologischer Symptome einhergehen kann. In den vergangenen Jahrzehnten wuchs in der Forschungsgemeinschaft die Erkenntnis, dass hier neben körperlichen Symptomen vor Allem auch kognitive Beeinträchtigungen vorliegen können. Aktuelle Studien berichten übereinstimmend Inzidenzraten von 45-60% (Amato, Zipoli & Portaccio, 2008). Da die Ausprägung dieser kognitiven Defizite einen erheblichen Einfluss auf den sozio-ökonomischen Status der Patienten hat, kommt ihrer Diagnostik ein hoher Stellenwert zu. Darüber hinaus stellen kognitive Beeinträchtigungen einen wichtigen Parameter zur Erfassung des Krankheitsverlaufs dar. Einige Studien berichten auch, dass das Vorliegen kognitiver Defizite bei MS einen wichtigen prognostischen Faktor für den weiteren Krankheitsverlauf darstellt (Kujala, Portin & Ruutiainen, 1997), und dass kognitive Defizite häufig bereits vor dem Vorliegen körperlicher Beeinträchtigungen objektivierbar sind (Stenager, Knudsen & Jensen, 1989).

Im Bereich der kognitiven Leistungsfähigkeit kann das klinische Bild von Beeinträchtigungen interindividuell stark variieren, so dass nicht verallgemeinernd vom Vorliegen oder der Abwesenheit kognitiver Beeinträchtigungen gesprochen werden sollte. Die Mehrzahl der Patienten mit neuropsychologischen Defiziten zeigen vielmehr eine Reihe diskreter bis mäßig ausgeprägter Teilleistungsbeeinträchtigungen. Ob es dabei ein MS-typisches, spezifisches Defizitprofil gibt, bleibt fraglich. Allerdings wird häufig gemutmaßt, dass die MS in erster Linie Auswirkungen auf die kortikale Interkonnektivität hat, was vermehrt zu Beeinträchtigungen bei solchen Aufgaben führt, die als 'schmutzige' Tests beschrieben werden könnten, da sie nicht ohne Weiteres einem bestimmten Konstrukt oder einer Teilleistung zugeordnet werden können.

In den letzten Jahren haben sich eine Vielzahl von Studien mit der Diagnostik kognitiver Defizite bei MS beschäftigt. Ein Schwerpunkt lag dabei auf der Etablierung neuropsychologischer Testbatterien, welche eine möglichst umfassende Leistungserfassung gewährleisten sollen. Einen weiteren Schwerpunkt stellte die Validierung neuropsychologischer Screening-Verfahren dar. Ziel dieser Screenings ist es, mit möglichst geringem diagnostischem Aufwand zunächst eine Aussage über das Vorliegen oder die Abwesenheit kognitiver Beeinträchtigungen zu fällen, um das weitere diagnostische Vorgehen zu bestimmen. Die Notwendigkeit hierzu ergibt sich aus der Tatsache, dass eine ausführliche neuropsychologische Diagnostik ausgesprochen zeit- und ressourcenaufwendig ist. Für viele Kliniken ist diese Form von Diagnostik schlichtweg nicht realisierbar, so dass sich der Bedarf nach ressourcenschonenden Alternativen ergibt, die gegebenenfalls sogar von nicht-psychologischem Klinikpersonal durchgeführt werden könnten.

Auch auf theoretischer Ebene erscheint dieser Ansatz vielversprechend: Während viele – aber keineswegs alle – MS-Patienten in den Tests der Screenings auffällige Ergebnisse erzielen, was auf eine allgemeine, der Krankheit zugrundeliegende Verlangsamung der Informationsverarbeitung zurückführbar sein könnte, finden sich in anschließend durchgeführten ausführlichen Testbatterien oft sehr differenzierte Ergebnisse, die eher gegen ein MS-typisches kognitives Defizitprofil sprechen.

Ziel der vorliegenden kumulativen Promotion ist es, zunächst einen detaillierten Überblick über die aktuellen Möglichkeiten und zur Verfügung stehenden Verfahren im Bereich der neuropsychologischen Diagnostik zu geben (Studie 1). Im Folgenden widmen sich die Studien 2 und 3 den Möglichkeiten neuropsychologischer Screening-Verfahren. Studie 2 validiert eine Kurzform der Brief Repeatable Battery (BRB), welche bereits seit mehreren Jahren im Zusammenhang mit MS zum Einsatz kommt. Studie 3 beschäftigt sich mit der Möglichkeit, diese Kurzform der BRB zu modifizieren. Ziel der Modifikation ist es, einen Ersatz für den Paced Auditory Serial Addition Test (PASAT) zu finden. Der PASAT war aus verschiedenen Gründen in den letzten Jahren als Diagnostikum in die Kritik geraten. Als Alternative im Rahmen der BRB wird der Fünf-Punkt-Test (FPT) diskutiert.

Es folgt zunächst eine detaillierte Schilderung des theoretischen Hintergrunds, sowie eine Beschreibung der durchgeführten Studien. Zuletzt folgt eine Zusammenfassung der Ergebnisse sowie eine übergreifende Diskussion.

2. Theoretischer Hintergrund

Multiple Sklerose ist eine entzündliche Erkrankung des Zentralen Nervensystems (ZNS: Gehirn und Rückenmark), welche sich schädigend auf Myelon und Axone auswirkt. Diese Entzündungen können abhängig von Lokalisation, Ausmaß und individuellen Ressourcen zu einer Vielzahl neurologischer Beeinträchtigungen führen, welche sich auf die Bereiche Sensorik, Motorik, Kontrolle autonomer Funktionen, affektives Erleben und Kognition beziehen. Der Erkrankungsbeginn liegt i.d.R. im jungen Erwachsenenalter zwischen 20 und 40 Jahren. Das Geschlechterverhältnis liegt für die meisten dokumentierten Verlaufsformen bei 3:1 (Frauen:Männer). Die Inzidenzrate wird aktuell in Deutschland mit etwa drei bis fünf Neuerkrankungen pro 100.000 Einwohner und Jahr beziffert (Diener et al., 2012).

2.1 Klinischer Verlauf

Etwa 80% der Patienten erleben einen initialen ‚Schub', d.h. eine akute Episode klinisch relevanter Beeinträchtigungen, welcher eine Phase der Symptommilderung bzw. vollständigen Remission folgt. Sofern diesem initialen Schub kein weiterer folgt, spricht man von einem klinisch isoliertem Syndrom (clinically isolated snydrome: CIS). Sofern es zu einem oder mehreren weiteren Schüben kommt, wird ggf. die Diagnose einer Multiplen Sklerose (MS) gestellt. Als Diagnosekriterien werden üblicherweise die McDonald-Kriterien herangezogen (Polman et al., 2005): Diese setzen voraus, dass zwei sowohl zeitlich als auch örtlich disseminierbare Läsionen im ZNS nachweisbar sind. Als bildgebendes Verfahren kommt dabei die Magnetresonanztomographie (MRT) mit T2-Gewichtung zum Einsatz. Wenn vom Patienten keine Phasen akuter Krankheitsaktivität berichtet werden, kann ein positiver MRT-Befund trotzdem zu einer MS-Diagnose führen. Weiterhin kann bei mehreren Schüben im Bereich desselben funktionellen Systems oder bei kontinuierlicher Progression der Symptomatik die MS-Diagnose auch durch den Nachweis oligoklonaler Banden in der zerebrospinalen Flüssigkeit erfolgen.

Drei Hauptformen der MS können unterschieden werden: (1) Der schubförmige Verlauf (relapsing-remitting multiple sclerosis: RRMS), von dem zu Beginn der Erkrankung die deutliche Mehrzahl der Patienten betroffen sind, ist durch Phasen akuter Krankheitsaktivität und anschließender Remission geprägt. Allerdings ist die Remission mit zunehmender Erkrankungsdauer zusehends unvollständig, so dass sich im Verlauf persistierende Symptome häufen. (2) Die Mehrzahl, nämlich etwa 65% der Patienten mit RRMS, gehen im weiteren Krankheitsverlauf in eine sekundär-progrediente MS (secondary-progressive MS: SPMS) über. Diese kann von weiteren Schüben begleitet werden, ist aber in erster Linie durch eine kontinuierliche Verschlechterung der Symptomatik gekennzeichnet. (3) Zuletzt leiden etwa 20% der Patienten von Erkrankungsbeginn an unter der primär chronisch-progredienten Verlaufsform (primary-progressive MS: PPMS), welche ebenfalls durch eine kontinuierliche Symptomverschlechterung definiert ist.

2.2 Ursachen der Multiplen Sklerose

Im Allgemeinen hat sich die Ansicht durchgesetzt, dass die Ursachen Multipler Sklerose sowohl in Umweltfaktoren als auch in einer genetischen Prädisposition zu finden sind (Compston & Coles, 2008). Beide Aspekte sollten daher gleichermaßen berücksichtigt werden.

2.2.1 Umweltfaktoren

Geographische Faktoren spielen möglicherweise eine Rolle beim Auftreten der MS: Generell zeigt sich, dass MS in den Ländern weit verbreitet ist, die sich weit vom Äquator entfernt befinden. Dies betrifft vor allem Europa, Nordamerika und Australien. Im Gegensatz dazu weisen afrikanische, südamerikanische und asiatische Länder eine vergleichsweise niedrigere Prävalenzrate auf (Kurtzke, 1975; Kurtzke, 1993). Somit zeigt sich, dass MS besonders stark dort verbreitet ist, wo sich Menschen europäischer Herkunft niedergelassen haben. Dieser Trend wird allerdings dadurch beeinflusst, wo Menschen mit erhöhtem Risiko, an MS zu erkranken, in ihren frühen Lebensjahren aufwachsen (Hammond, English & McLeod, 2000). So führt ein Umzug in der Kindheit von einem Gebiet mit hohem Risiko, an MS zu erkranken, in ein Gebiet mit niedrigem Risiko, zu einem verringerten Erkrankungsrisiko im Vergleich zur Ausgangspopulation.

Des Weiteren wurde die sogenannte Hygiene-Hypothese ins Gespräch gebracht: Demnach stellt eine frühe Ansteckung mit infektiösen Krankheiten wie Masern, Mumps, Röteln oder dem Epstein-Barr-Virus einen Schutzfaktor dar. Tritt eine entsprechende Infektion jedoch erst relativ spät im Leben - in der Regel im jungen Erwachsenenalter - auf, kommt es möglicherweise zu einer fehlgeleiteten Antwort des Immunsystems, welche zu MS führt (Martyn, Cruddas & Compston, 1993). Dies wurde zumindest theoretisch anhand des Epstein-Barr-Virus nachgewiesen (Lang et al., 2002), und eine späte Infektion mit dem Epstein-Barr-Virus erhöhte tatsächlich in einer großen epidemiologischen Studie die Wahrscheinlichkeit, an MS zu erkranken (Levin et al., 2003).

2.2.2 Genetische Faktoren

Die alterskorrigierte Wahrscheinlichkeit, als weißer Nordeuropäer an MS zu erkranken, beträgt ca. 0,3% (Compston & Coles, 2008). Im Gegensatz dazu erhöht sich das Risiko, wenn Verwandte ersten Grades eine MS-Erkrankung aufweisen, ebenfalls an MS zu erkranken, auf bis zu 5% (bei erkrankten Geschwistern) bzw. 2% (bei einem erkrankten Elternteil) (Robertson, Clayton, Fraser, Deans & Compston, 1996; Carton et al., 1997). Bei Zwillingen ist das Risiko, an MS zu erkranken, wenn ein Geschwister an MS erkrankt ist, noch einmal deutlich höher und wird für monozygote Zwillinge mit bis zu 25% angegeben (Willer, Dyment, Risch, Sadovnick & Ebers, 2003). Kinder, deren Adoptiveltern oder Adoptivgeschwister an MS erkrankten, zeigen kein erhöhtes Risiko, selbst an MS zu erkranken (Ebers, Sadovnick & Risch, 1995; Dyment, Yee, Ebers & Sadovnick, 2006). Zusammengenommen ergeben sich somit recht deutliche Hinweise auf einen familiären beziehungsweise genetischen Einfluss auf das Risiko, an MS zu erkranken. Als assoziierte Gene wurden dabei unter anderem HLA Klasse I und II, T-Zell-Rezeptor β, CTLA4, ICAM1 und SH2D2A identifiziert.

2.3 Neuropathologie

Sichtbares Zeichen der MS sind Entmarkungsherde oder Plaques im zentralen Nervensystem. Diese stellen den Endzustand eines Prozesses dar, der mit einer Entzündung im zentralen Nervensystem beginnt. Diese Entzündungen können der Erstmanifestation von neurologischen oder neuropsychologischen Symptomen zum Teil um Jahre vorausgehen. Im Rahmen der Entzündung greifen Lymphozyten die Myelinscheiden der Nervenbahnen an. Diese Demyelinisierung führt zunächst zu einer Reduktion der neuronalen Leitungsgeschwindigkeit. Obwohl in frühen Phasen der Erkrankung eine Remyelinisierung der Nervenbahnen beziehungsweise auch eine Restrukturierung der betroffenen axonalen Verbindungen nach Abklingen der Entzündung möglich ist, führt der sich wiederholende Prozess von Aufflammen und Abklingen der Entzündung letztlich zu einer irreversiblen Schädigung der axonalen Verbindungen des ZNS. Die Ursache dieser scheinbar fehlgeleiteten Immunantwort der Lymphozyten, die sich gegen körpereigene Strukturen richtet, bleibt trotz zahlreicher Forschungsansätze unklar (Compston & Coles, 2008).

2.4 Neuropsychologische Defizite bei Multipler Sklerose

Die Mehrzahl der physischen Symptome bei MS wie zum Beispiel Schwäche, Steifigkeit, mangelnde Koordination, Gangstörungen, neurogene Blasenstörungen, Sehstörungen, Sensibilitätsstörungen oder sexuelle Dysfunktionen lassen sich spezifischen Läsionslokalisationen im zentralen Nervensystem zuordnen (Chelune, Stott & Pinkston, 2008). Dies gilt jedoch nicht für kognitive Defizite: Neurophysiologische Veränderungen können zwar mit modernen bildgebenden Verfahren relativ zuverlässig dargestellt werden, korrelieren jedoch bestenfalls mäßig mit der Lokalisation kognitiver Beeinträchtigungen (Hoffmann, Tittgemeyer & von Cramon, 2007). Vielmehr scheint die allgemeine kortikale Läsionslast einen besseren Prädiktor der kognitiven Beeinträchtigungen darzustellen (Calabrese et al., 2009). Aufgrund der erheblichen Alltagsrelevanz kognitiver Leistungen im Zusammenhang mit der beruflichen Leistungsfähigkeit und selbstständigen Lebensführung, sowie aufgrund der Tatsache, dass ca. 45 bis 65% aller MS-Patienten im Laufe ihrer Erkrankung kognitive Beeinträchtigungen entwickeln (DeSousa, Albert & Kalman, 2002), kommt der neuropsychologischen Diagnostik somit eine wichtige Rolle bei der Beurteilung des Krankheitsverlaufs und der Auswirkungen der neurophysiologischen Veränderungen zu. Folglich empfehlen auch die aktuellen Leitlinien der Deutschen Gesellschaft für Neurologie eine neuropsychologische Diagnostik bereits zu Beginn der Erkrankung sowie regelmäßige Verlaufskontrollen (Gold, Wiendl & Hemmer, 2014).

Die Ausprägung dieser kognitiven Beeinträchtigungen kann dabei ausgesprochen unterschiedlich ausfallen. So fanden sich bei Patienten mit schubförmig-remittierender MS drei distinkte Muster neuropsychologischer Beeinträchtigungen (Ryan, Clark, Klonoff, Li & Paty, 1996; Fischer, Jacobs, Cookfair & Rudick, 1998). Während 34-46% der Patienten aus neuropsychologischer Sicht zumindest oberflächlich keine Auffälligkeiten zeigten, waren etwa ein Sechstel aller Patienten derart deutlich beeinträchtigt, dass sie in mindestens drei kognitiven Domänen zumindest moderate Beeinträchtigungen aufwiesen. Die häufigste Gruppe stellten mit 37-49% aller Patienten jedoch jene, die nur leichte oder eng umrissene Beeinträchtigungen in einzelnen kognitiven Funktionsbereichen aufwiesen. Die Tatsache, dass sich hierbei kein MS-typisches Defizitprofil zeigte, macht daher die Untersuchung mehrerer kognitiver Funktionen erforderlich (Lezak, 2012). Besonderes Augenmerk wird dabei auf folgende Leistungsbereiche gelegt:

1. *Aufmerksamkeit*

   Der nach heutigem Kenntnisstand häufigste Befund neuropsychologischer Beeinträchtigungen bei MS-Patienten ist eine verminderte Informationsverarbeitungsgeschwindigkeit (Archibald & Fisk, 2000; DeLuca, Chelune, Tulsky, Lengenfelder & Chiaravalloti, 2004; Bergendal, Fredrikson & Almkvist, 2007). Dieses Defizit spielt sowohl bei Aufgaben mit Speed-Komponente als auch bei solchen Aufgaben, die kortiko-kortikale Konnektivität erfordern, eine Rolle (Lynch, Dickerson & Denney, 2010) und kommt besonders bei Aufgaben mit höherer Komplexität bzw. höherem Anforderungscharakter zum Tragen. Beispiele hierfür sind Aufgaben zur geteilten Aufmerksamkeit oder Aufgaben mit regelmäßigem Wechsel des Antwortfokus (Paul, Beatty, Schneider, Blanco & Hames, 1998; Archibald & Fisk, 2000) Demgegenüber sind einfache Aufmerksamkeitsleistungen wie Spannenmaße in der Regel unbeeinträchtigt (Rao, Leo, Bernardin & Unverzagt, 1991).

2. *Gedächtnis*

   Auch Gedächtnisleistungen zählen zu den am häufigsten beeinträchtigten kognitiven Funktionen bei MS-Patienten (Rao et al., 1993), wobei sich dies neueren neuropsychologischen Studien zufolge in erster Linie auf die Informationsaufnahme und weniger auf den Abruf bezieht (DeLuca, Gaudino, Diamond, Christodoulou & Engel, 1998; Chiaravalloti, Balzano, Moore & DeLuca, 2009; Stegen et al., 2010). Somit erweisen sich sowohl bestehende implizite als auch explizite Gedächtnisinhalte bei MS-Patienten als intakt, und Defizite zeigen sich in der Regel nur bei der Akquisition neuer Informationen. MS-Patienten benötigen mehr Lerndurchgänge beim Lernen einer Wortliste, doch sobald dasselbe Niveau wie bei Gesunden erreicht ist, unterscheiden sich Abruf- und

Rekognitionsleistung nicht maßgeblich von der Leistung Gesunder (Chiaravalloti et al., 2009; Stegen et al., 2010).

3. *Exekutivfunktionen*

Exekutivfunktionen beinhalten eine Reihe von Teilleistungen wie logisches Denken, Handlungsplanung, Inhibition, kognitive Flexibilität oder Produktivität (z.B. Strauss, Sherman & Spreen, 2006; Lezak, 2012). Gleichzeitig wird ihnen ein Anteil an anderen kognitiven Funktionen wie Arbeitsgedächtnis und komplexen Aufmerksamkeitsleistungen zugeschrieben, und Beeinträchtigungen im Bereich der Exekutivfunktionen sind häufig mit Defiziten in anderen kognitiven Domänen konfundiert (Gauggel & Sturm, 2005). Bereits als es in der Forschungsgemeinschaft ein gewachsenes Bewusstsein für die häufige Prävalenz kognitiver Beeinträchtigungen bei MS-Patienten gab, wurden Defizite im Bereich der Exekutivfunktionen tendenziell unterschätzt (Rao et al., 1991; Fischer et al., 1994). Neuere Studien kommen weitgehend übereinstimmend zu dem Schluss, dass auch Beeinträchtigungen im Bereich der Exekutivfunktionen zu den häufig bei MS vorkommenden kognitiven Defiziten zählen (Denny, Sworowski & Lynch, 2005; Parmenter et al., 2007; Drew, Tippett, Starkey & Isler 2008).

4. *Visuo-räumliche Funktionen*

MS-bedingte Beeinträchtigungen der Sehfähigkeit sollten nicht mit dem Vorliegen visuo-räumlicher Funktionsstörungen verwechselt werden, und in den meisten Fällen lassen sich Beeinträchtigungen im Bereich visuo-perzeptiver und visuo-konstruktiver Leistungen vermutlich auf eine persistierende Beeinträchtigung im Bereich des Sehnervs zurückführen (Jasse et al., 2013). Dennoch gibt es überzeugende Hinweise darauf, dass visuo-räumliche Funktionen bei einer kleinen Zahl von MS-Patienten auch unabhängig von der Sehfähigkeit beeinträchtigt sein können (Moreno, García, Marasescu, González & Benito, 2013), so dass auch eine Berücksichtigung dieses Leistungsbereichs im Rahmen einer neuropsychologischen Diagnostik sinnvoll erscheint.

2.5 Spezifische Neuropsychologische Diagnostik bei MS

Wie in den vorherigen Abschnitten bereits angedeutet wurde, scheint es im Rahmen der neuropsychologischen Diagnostik bei MS einen bemerkenswerten Dualismus zu geben: Einerseits wird davon ausgegangen, dass es kein MS-typisches Defizitprofil gibt (Ryan et al., 1996; Fischer et al., 1998; Lezak, 2012), was folglich die Durchführung einer ausführlichen Testbatterie rechtfertigen würde, um alle denkbarerweise betroffenen kognitiven Domänen abzudecken. Andererseits wird immer wieder von verschiedenen Quellen die Beobachtung geäußert, dass es insbesondere die Informationsverarbeitungsgeschwindigkeit sein dürfte, die bei MS betroffen ist (Archibald & Fisk, 2000; DeLuca et al., 2004; Bergendal et al., 2007; Hoffmann et al., 2007). Als Ursachen hierfür werden Schädigungen der langen Faserbahnen angeführt, welche schließlich zu einer Beeinträchtigung der kortiko-kortikalen Konnektivität und in der Konsequenz zu einer kognitiven (und auch motorischen) Verlangsamung führen.

Dieser Dualismus findet sich auch in den neuropsychologischen Untersuchungsmethoden. Während sogenannte Screening-Verfahren bei MS üblicherweise eine erkennbare Fokussierung auf Informationsverarbeitungsgeschwindigkeit legen, sollen ausführliche Testbatterien alle einzelnen kognitiven Domänen möglichst unkonfundiert erfassen. Hierbei handelt es sich nur scheinbar um einen Widerspruch: Nimmt man an, dass die Hypothese der kortiko-kortikalen Dyskonnektivität die Realität angemessen abbildet, so ist eine verringerte Informationsverarbeitungsgeschwindigkeit möglicherweise ein universelles oder zumindest federführendes Defizit bei MS. Gleichzeitig ist die individuelle Läsionslast und –verteilung von Patient zu Patient sehr unterschiedlich, was dazu führt, dass sich diese Verlangsamung sehr unterschiedlich äußern kann. Gleiches gilt auch für die Betrachtung individueller kognitiver Ressourcen und Kompensationspotential. Somit ist der orientierende Befund einer Verlangsamung der Informationsverarbeitungsgeschwindigkeit zwar Ausdruck einer kognitiven Beeinträchtigung aufgrund kortikaler Schädigung, erlaubt aber noch keine Rückschlüsse über das Abschneiden in domänenspezifischen neuropsychologischen Tests oder gar über das Vorliegen einer Alltagsrelevanz. Der Umkehrschluss, dass ein unauffälliger neuropsychologischer Befund im Bereich der Informationsverarbeitungsgeschwindigkeit immer Symptomfreiheit bedeutet, kann im Falle der MS ebenfalls nicht ohne weiteres getroffen werden, da neben allgemeiner kortiko-kortikaler Dyskonnektivität mitunter eben doch domänenspezifische kortikale Areale stärker geschädigt sein können. Um diesem Sachverhalt gerecht zu werden, erfassen die üblicherweise bei MS zum Einsatz kommenden Screenings nicht nur die Informationsverarbeitungsgeschwindigkeit, sondern in geringem Umfang auch eine oder zwei andere kognitive Domänen wie Gedächtnis und Exekutivfunktionen. Inwieweit die hier vorgefundenen Testkonstellationen als sinnvoll oder inhaltlich valide anzusehen sind, ist allerdings noch Diskussionsgegenstand.

Ein zweistufiges Vorgehen mit initialem Screening zur Überprüfung der Frage, ob sich Beeinträchtigungen im Bereich der Informationsverarbeitungsgeschwindigkeit finden oder nicht, um bei Bedarf eine ausführliche Testbatterie anzuschließen, erscheint speziell bei MS insofern sinnvoll. Sollte sich aufgrund anderer Erwägungen wie Auffälligkeiten in Anamnese und Exploration oder subjektiven Beschwerdeschilderungen ein Anfangsverdacht auf das Vorliegen kognitiver Defizite ergeben, kann von diesem Prozedere abweichend natürlich dennoch eine ausführliche Diagnostik angeschlossen werden. Bei diesen Erwägungen spielen dann auch häufig ökonomische Gesichtspunkte wie die Verfügbarkeit eines qualifizierten Neuropsychologen eine Rolle. Auf die Beschaffenheit der hier angesprochenen Screenings und ausführlichen Testbatterien wird im Rahmen dieser Dissertation im Weiteren näher und differenzierter eingegangen werden.

3. Ziele der Dissertation

Wie oben ausgeführt, kommt der neuropsychologischen Diagnostik im Rahmen der MS eine wichtige Rolle zu. Die überwiegende Mehrzahl der kognitiven Defizite, die bei MS dokumentiert sind, kann dabei einer der vier bereits vorgestellten kognitiven Domänen zugeordnet werden (Aufmerksamkeit, Gedächtnis, Exekutivfunktionen, visuo-räumliche Funktionen). Bei der ersten Studie im Rahmen dieser Dissertation handelt es sich um eine Übersichtsarbeit, welche zum Ziel hat, einen ausführlichen Überblick über die in den einzelnen Domänen zum Einsatz kommenden neuropsychologischen Untersuchungsverfahren zu geben. Der Schwerpunkt der Beobachtung liegt dabei auf der Frage, inwiefern die jeweiligen Verfahren sich speziell zur Diagnosestellung bei MS eignen, und ob sie sich gegebenenfalls bereits als Diagnostikum bei MS bewährt haben.

Aus ökonomischen Gründen kann eine ausführliche Diagnostik allerdings oft nicht flächendeckend angeboten werden. Eine mögliche Alternative zu ausführlichen neuropsychologischen Testbatterien stellen Screening-Verfahren dar. Ziel solcher Screenings ist es, mit möglichst geringem Aufwand eine möglichst genaue Aussage über das Vorliegen oder die Abwesenheit kognitiver Beeinträchtigungen zu treffen, um dann bei Bedarf in einem zweiten Schritt eine ausführliche Diagnostik zur weiteren Differenzierung anschließen zu können. Grundvoraussetzung dafür ist die korrekte Identifizierung besonders indikativer Tests und für MS spezifischer Teilleistungsbeeinträchtigungen. Wie bereits erwähnt, finden sich auf Ebene ausführlicher Testbatterien solche spezifischen Teilleistungsbeeinträchtigungen eher nicht. Allerdings gibt es Hinweise darauf, dass eine verringerte Informationsverarbeitungsgeschwindigkeit aufgrund kortiko-kortikaler Dyskonnektivität als Kardinalsymptom kognitiver Dysfunktion bei MS angesehen werden kann (Hoffmann et al., 2007). Dementsprechend haben die im Folgenden diskutierten Screening-Verfahren einen hohen Anteil an Testverfahren, die Informationsverarbeitungsgeschwindigkeit erfassen oder damit konfundiert sind. Eines dieser Screening-Verfahren stellt eine Kurzform der Brief RepeatableBattery (BRB: Rao, 1990) dar, welche von Portaccio et al. (2009) validiert wurde und den PacedAuditory Serial Addition Test (PASAT: Strauss et al., 2006), den Symbol Digit Modalities Test (SDMT: Smith, 1982) und den Selective Reminding Test (SRT: Buschke & Fuld, 1974) beinhaltet. Als methodisch fragwürdig ist bei dieser Validierung zu kritisieren, dass das Screening-Verfahren und der herangezogene Goldstandard teilweise redundant waren, so dass eine artifizielle Erhöhung von Sensitivität und Spezifität nicht ausgeschlossen werden konnten. Ziel der ersten empirischen Studie war es daher, die Ergebnisse von Portaccio et al. (2009) zu überprüfen. Diese Überprüfung von Sensitivität und Spezifität der Kurzform der BRB fand anhand eines unabhängigen Goldstandards statt.

In der zweiten empirischen Studie wurde überprüft, ob die Kurzform der BRB weiterhin ein prädiktiver Indikator für kognitive Beeinträchtigungen bei MS bleibt, wenn man sie hinsichtlich ihrer Komposition leicht modifiziert. Konkret wurde der PASAT ersetzt, da sich dieser Test wiederholter Kritik ausgesetzt sieht: Es bestehen Bedenken hinsichtlich der Unklarheit bezüglich der von ihm erfassten Konstrukte, und er wird von Patienten häufig als stressintensiv und fordernd empfunden. Als alternatives Verfahren kam der Fünf-Punkt Test (FPT: Regard, Strauss & Knapp, 1982) zum Einsatz.

Das übergeordnete Ziel beider Studien ist somit die Klärung der Fragestellung, ob die konzipierten Screening-Verfahren, obwohl sie nur einen vergleichsweise kleinen Ausschnitt kognitiver Leistungen abbilden, dennoch so konstruiert sind, dass sie eine valide Prognose über das Vorliegen oder die Abwesenheit kognitiver Beeinträchtigungen erlauben.

4. Eigene Arbeiten

4.1 Übersichtsarbeit: Neuropsychologische Diagnostik bei MS

Hansen, S. & Lautenbacher, S. (2017) Neuropsychological assessment in multiple sclerosis: an overview. Zeitschrift für Neuropsychologie, 28 (2), 117-148

4.1.1 Zielsetzung und Methodik

Ziel der Arbeit war es, einen Überblick über neuropsychologische Diagnoseverfahren zu geben und dem Diagnostiker eine Entscheidungshilfe hinsichtlich der Anwendbarkeit spezifischer Prozeduren zu geben. Außerdem sollten Studiendaten zu spezifischen Diagnoseverfahren im Kontext der MS vorgestellt und zusammengefasst werden. Abschließend sollten aufgrund der Ergebnisse der Übersichtsarbeit Empfehlungen zur Zusammenstellung von Screeningverfahren und ausführlichen Testbatterien gegeben werden.

Als Grundlage der vorliegenden Arbeit dienten Übersichtsartikel unter Anderem von DeSousa (2002), Calabrese (2006) und Chiaravalloti und DeLuca (2008). Die Datenbank PubMed wurde konsultiert, um weitere relevante Studien zu ermitteln. Aus den Literaturverzeichnissen der so rekrutierten Literatur ergaben sich gegebenenfalls Hinweise auf weiterführende relevante Literatur. Obwohl eine große Zahl auch relativ aktueller Übersichtsartikel zum Thema Kognition bei MS ermittelt werden konnte, beschäftigten sich doch nur sehr wenige dieser Artikel mit dem Thema der Komposition einer Testbatterie bei MS. Der aktuellste Artikel in diesem Zusammenhang (Benedict et al., 2002) beschäftigt sich mit der Konstruktion einer Testbatterie anhand der Testpräferenzen einer Expertenkommission, dem Minimal Assessment of Cognitive Function in MS (MACFIMS). Ein Abwägen einzelner Tests oder deren kritische Würdigung als Diagnostikum im Zusammenhang mit MS vermisst man jedoch auch hier. Weiterhin fiel auf, dass nur sehr wenige Reviews eine differenzierte Analyse auf Testebene vollzogen, und diese wenigen Studien bereits als etwas älter einzustufen sind (Zakzanis, 2000; Potagas et al., 2008). Hieran wird die Notwendigkeit einer aktuellen Übersichtsarbeit zu diesem Thema ersichtlich.

Folglich wurde zunächst ein kurzer Überblick über die Einflussfaktoren auf die kognitive Leistungsfähigkeit bei MS gegeben. Anschließend wurden die vier bereits erwähnten kognitiven Domänen (Aufmerksamkeit, Gedächtnis, Exekutivfunktionen und visuo-räumliche Funktionen) besprochen. Dabei wurden in der Literatur einschlägige Diagnoseverfahren hinsichtlich ihrer Anwendbarkeit bei MS vorgestellt und gegeneinander abgewogen. Außerdem wurden auch weniger bekannte Diagnoseverfahren zur Sprache gebracht, zu denen ebenfalls Daten im Zusammenhang mit MS-Patienten vorliegen. Zuletzt wurden die gesammelten Informationen genutzt, um ein diagnostisches Prozedere zu konstruieren, welches zum Ziel hat, möglichst ökonomisch zu testen und dabei trotzdem alle möglicherweise betroffenen Teilleistungsbereiche abzudecken.

4.1.2 Ergebnisse

4.1.2.1 Einflussfaktoren auf die kognitive Leistungsfähigkeit bei MS

Wie bereits erwähnt, zeigen sich bei etwa 45-65% aller MS-Patienten Hinweise auf kognitive Beeinträchtigungen in neuropsychologischen Untersuchungen. Diese Zahlen sind jedoch abhängig von den durchgeführten Testverfahren sowie den zugrundegelegten statistischen Kriterien. Als Einflussfaktor wird die Verlaufsform der MS diskutiert - wobei der chronisch-progredienten Form im Allgemeinen ein deutlicherer Einfluss auf die kognitive Leistungsfähigkeit zugeschrieben wird (Potagas et al., 2008). Weitere dokumentierte Einflussfaktoren sind die Erkrankungsdauer (Amato, Zipoli & Portaccio, 2006) und die allgemeine Läsionslast (Comi, Rovaris, Leocani, Martinelli & Filippi, 2000). Auch das Geschlecht spielt möglicherweise eine Rolle bei der Ausprägung der kognitiven Defizite, wobei Männer mutmaßlich häufiger betroffen sind als Frauen (Savettieri et al., 2004). Daneben sollten auch Depressivität (Beblo & Lautenbacher, 2006) und kognitive Fatigue (Shah, 2009) als konfundierende Variablen in Betracht gezogen werden, da beide häufig im Zusammenhang mit MS auftreten und beide die kognitive Leistungsfähigkeit potentiell negativ beeinflussen.

4.1.2.2 Kognitive Domänen

4.1.2.2.1 Aufmerksamkeit

Wie bereits erwähnt, zählen Aufmerksamkeitsfunktionen wie die Informationsverarbeitungsgeschwindigkeit zu den am häufigsten bei MS beeinträchtigten kognitiven Funktionen. Als Testverfahren haben sich in diesem Leistungsbereich vor allem kurze, nicht-computerisierte Verfahren etabliert. Die größte Verbreitung dürfte der Symbol Digit Modalities Test (SDMT: Smith, 1982) haben. Er ist Bestandteil von zwei häufig verwendeten kognitiven Screenings, nämlich der Brief Repeatable Battery (BRB: Rao, 1990) und des jüngeren Brief International Cognitive Assessment for MS (BICAMS: Langdon et al., 2012). Im SDMT muss der Patient anhand einer vorgegebenen Legende verbale Paarungen von Zahlen zu Symbolen vornehmen. Der Test ist insofern dem Zahlen-Symbol-Test aus der Wechsler Adult Intelligence Scale (WAIS: Wechsler, 2008) ähnlich. Studienübergreifend werden dem SDMT eine hohe Reliabilität und eine hohe Validität attestiert. Sonder, Burggraaff, Knol, Polman und Uitdehaag (2014) identifizierten den SDMT als den einzelnen Test mit dem höchsten prädiktiven Wert in Bezug auf die Aussage über das Vorliegen einer kognitiven Beeinträchtigung.

Ein weiterer wichtiger und in der MS-Literatur häufig anzutreffender Test im Zusammenhang mit Aufmerksamkeitsfunktionen ist der Paced Auditory Serial Addition Test (PASAT: Strauss et al., 2006). Auch der PASAT ist Bestandteil der BRB, und außerdem der einzige kognitive Parameter im Multiple Sclerosis Functional Composite (MSFC: Fischer, Rudick, Cutter & Reingold, 1999), einem klinischen Verlaufsparameter bei MS. Beim PASAT muss der Patient auditiv in einem fixierten Intervall präsentierte Zahlen addieren, wobei jeweils die Summe der beiden zuletzt gehörten Zahlen genannt werden muss. Anhand dieser Beschreibung ist bereits ersichtlich, dass der PASAT eine Reihe kognitiver Teilleistungen erfordert: Neben Aufmerksamkeitsleistungen im Sinne von

Informationsverarbeitungsgeschwindigkeit und phonologischer Spanne sind auch eher dem Bereich der Exekutivfunktionen zuzuordnende Arbeitsgedächtnisleistungen erforderlich. Zuletzt spielen auch mathematische Fähigkeiten eine Rolle bei der erfolgreichen Aufgabenbearbeitung. Aufgrund dieser Konfundierung der zugrundeliegenden Funktionsbereiche sowie aufgrund der Tatsache, dass er von Patientin oft als belastend und enervierend empfunden wird, und in einzelnen Fällen die Teilnahme abgelehnt wird, ist der PASAT kontinuierlicher Kritik ausgesetzt. Die Tatsache, dass er immer noch regelmäßig als klinischer Outcomeparameter zum Einsatz kommt, spricht jedoch für seine Bedeutung in diesem Zusammenhang.

Daneben kommt auch computergestützten Verfahren eine wichtige Rolle bei der Diagnostik von Aufmerksamkeitsfunktionen bei MS zu, allerdings ist die Datenlage hierzu eher begrenzt. Eine mögliche Erklärung hierfür findet sich in der Tatsache, dass viele MS-Patienten aufgrund ihrer motorischen Beeinträchtigungen per se Schwierigkeiten im Bereich der psychomotorischen Geschwindigkeit haben, was die Aussagekraft computergestützter Verfahren, die in der Regel das rasche und richtige Reagieren anhand eines Tastendrucks messen, reduziert. Dennoch sollte insbesondere bei spezifischen Fragestellungen wie zum Beispiel im Bereich der Kraftfahreignung eine ausführliche neuropsychologische Diagnostik auch computerisierte Verfahren beinhalten. Insbesondere in der europäischen Literatur findet sich dabei in Bezug auf MS immer wieder die Testbatterie zur Aufmerksamkeitsprüfung (TAP: Zimmermann & Fimm, 2009).

4.1.2.2.2 Gedächtnis

Auch Gedächtnisleistungen erweisen sich bei MS-Patienten als häufig beeinträchtigt. Wie bereits im Theorieteil geschildert, betrifft dies insbesondere Neugedächtnisleistungen im Sinne einer reduzierten Aufnahmekapazität, so dass MS-Patienten über dieselbe Anzahl Lerndurchgänge weniger Informationen aufnehmen können als gesunde Kontrollprobanden. Als besonders indikativ für Gedächtnisprobleme bei MS haben sich Tests zum Listenlernen erwiesen. Erwähnenswert sind in diesem Zusammenhang der Selective Reminding Test (SRT: Buschke & Fuld, 1994), der auch Bestandteil der BRB ist, sowie der California Verbal Learning Test (CVLT: Niemann, Sturm, Thöne-Otto & Willmes, 2008), der seinerseits Teil des BICAMS und des MACFIMS ist. Sowohl der SRT als auch der CVLT kommen international zur Anwendung und haben sich als Diagnostikum bei MS bewährt. Eine Aussage darüber zu treffen, welches der beiden Testverfahren die Gedächtnisleistung von MS-Patienten besser einschätzen kann, dürfte unmöglich sein. Trotzdem muss festgehalten werden, dass – obwohl beide Testverfahren auf dem Prinzip des Listenlernens fußen – der SRT und der CVLT sich paradigmatisch unterscheiden: Während im CVLT bei jedem Durchgang die komplette Wortliste wiederholt wird, werden im SRT bei jedem Durchgang nur die Begriffe wiederholt, welche der Proband bei der letzten Reproduktion nicht nennen konnte. Insofern kann es vorkommen, dass Patienten Auffälligkeiten nur bei einem der beiden Verfahren zeigen, was insbesondere bei grenzwertigen Ergebnissen in einem der Verfahren auch die Durchführung des zweiten Verfahrens indiziert.

Neben Tests zum verbalen Neugedächtnis haben auch einige Verfahren zum nonverbalen Neugedächtnis Eingang in die neuropsychologische Diagnostik bei MS gefunden. Vor allem ist dabei der Brief Visuospatial Memory Test (BVMT: Benedict, 1997) zu nennen, der fester Bestandteil der

BICAMS und des MACFIMS ist. Sechs geometrische Formen werden dem Patienten dreimal für jeweils zehn Sekunden präsentiert, woraufhin der Patient jeweils im Anschluss eine Gedächtniskopie der Muster anfertigt. Ein verzögerter Abruf erfolgt nach 20 Minuten. Die aktuelle Studienlage attestiert dem BVMT eine hohe Reliabilität und Validität bei MS-Patienten und weist ihn insbesondere als überlegen gegenüber anderen Verfahren zum nonverbalen Neugedächtnis wie der Rey-Figur (Rey, 1941) und dem Spatial Recall Test (Rao, Hammeke, McQuillen, Khatri & Lloyd, 1984) aus.

4.1.2.2.3 Exekutivfunktionen

Exekutivfunktionen stellen ein breites Feld neuropsychologischer Teilleistungen dar, und sind insofern in Gänze unter Umständen nur schwer in einer neuropsychologischen Testbatterie abzubilden. Umso verwunderlicher ist es, dass sie in den einschlägigen neuropsychologischen Screenings und Testbatterien zu MS (BRB, BICAMS, MACFIMS) nur unzureichend vertreten sind. Das Argument, dass Defizite in Verfahren zu Exekutivfunktionen häufig mit Beeinträchtigungen im Bereich der psychomotorischen Geschwindigkeit zusammenhängen, verfängt nicht, da sich für nahezu jede exekutive Teilleistung auch ein Paradigma ohne Speed-Komponente findet.

Neben dem PASAT, der in der aktuellen Arbeit auch als Verfahren zur Informationsverarbeitungsgeschwindigkeit deklariert wurde, ist der am intensivsten erforschte Test zu Exekutivfunktionen bei MS vermutlich der Wisconsin Card Sorting Test (WCST: Heaton, Chelune, Curtiss, Kay & Talley, 1993). Hierbei muss der Patient einen Satz von Karten anhand einer bestimmten, dem Patienten zunächst unbekannten Regel sortieren. Sobald diese Regel von dem Patienten erkannt und konsequent angewendet wird, ändert sich jedoch die Regel ohne sein Wissen, und der Patient muss sein Vorgehen entsprechend anpassen. Obwohl der WCST studienübergreifend gut zwischen MS-Patienten und Gesunden differenziert, findet er sich kaum in aktuellen Studien zu MS und Kognition. Der maßgebliche Grund hierfür dürfte in seiner Länge liegen: Eine Testung mit dem WCST kann bis zu einer Stunde Zeit in Anspruch nehmen. So hat sich im MACFIMS die Kurzform einer Variante dieses Tests etabliert, deren prognostische Validität im Zusammenhang mit MS jedoch noch weitgehend ungeklärt ist.

Weitere Testverfahren, welche regelmäßig bei MS zur Anwendung kommen, sind verbale Produktivitätstests. Bei diesen muss der Patient innerhalb einer begrenzten Zeit möglichst viele Begriffe nennen, die ein vorgegebenes Zielkriterium erfüllen. In der Regel handelt es sich um die Vorgabe einer Kategorie oder eines Anfangsbuchstabens. Diese Produktivitätstests haben sich in der Mehrzahl der Studien als ausgesprochen indikativ erwiesen und sind konsequenterweise ebenfalls Bestandteil des MACFIMS. Allerdings bleibt – ähnlich wie beim PASAT – auch hier unklar, welches neuropsychologische Konstrukt tatsächlich mit der abgeprüften Testleistung erfasst wird. Es ist insofern fraglich, ob Tests zu verbaler Produktivität eher Exekutivfunktionen im Sinne von ‚Ideenflüssigkeit' oder vielmehr Arbeitsgeschwindigkeit oder Wortschatz überprüfen.

Daneben gibt es noch eine Reihe weiterer Tests zu Exekutivfunktionen, die über mehrere Studien und Jahrzehnte hinweg immer wieder zur neuropsychologischen Diagnostik bei MS eingesetzt wurden. Besonders hervorzuheben wären solche Untersuchungsverfahren, welche ein Stroop-Paradigma beinhalten, sowie nonverbale Planungsaufgaben wie zum Beispiel der Turm von London

(Tucha & Lange, 2004). Gleichwohl muss bemerkt werden, dass die Befunde zur diagnostischen Validität der letztgenannten Untersuchungsverfahren bei MS eher zweigeteilt sind, und einige Studien finden bei diesen Verfahren für MS-Patienten im Vergleich zu gesunden Kontrollprobanden kaum Unterschiede in der Ausprägung der Zielkriterien.

4.1.2.2.4 Visuo-räumliche Funktionen

Im Vergleich zu den bereits diskutierten kognitiven Domänen dürften visuo-räumliche Funktionen bei MS-Patienten eher selten beeinträchtigt sein. Viele der von den Patienten subjektiv berichteten Beeinträchtigungen beim ‚Sehen' als Wahrnehmungsleistung dürften mit Entzündungen des Sehnervs und einer tatsächlichen MS-bedingten Beeinträchtigung der Sehfähigkeit in Verbindung stehen. Dennoch sind einige Fälle von Patienten mit ausgeprägten visuo-räumlichen Funktionsstörungen dokumentiert, was den Einsatz orientierender Verfahren für diesen Leistungsbereich rechtfertigt. Die MACFIMS beinhaltet zu diesem Zweck den Judgment of Line Orientation Test (JLO: Benton, 1994). Es handelt sich um ein kurzes Verfahren, bei dem der Patient die Orientierung zweier gerader Linien beurteilen muss. Aufgrund des eher seltenen Auftretens von visuo-räumlichen Funktionsstörungen kann dies als hinreichend angesehen werden. Sollten sich jedoch Hinweise auf Beeinträchtigungen in diesem Leistungsbereich ergeben, empfiehlt sich die Durchführung einer differenzierteren Testbatterie visueller Wahrnehmung wie der Visual Object and Space Perception Battery (VOSP: Warrington & James, 1991).

4.1.3 Zusammenfassung

Aufgrund der häufig bei MS-Patienten vorkommenden kognitiven Beeinträchtigungen und deren potentieller Alltagsrelevanz empfiehlt sich in jedem Fall die Durchführung einer neuropsychologischen Diagnostik. Hierfür hat sich in den vergangenen Jahren eine Reihe von Verfahren etabliert. Zwar befinden sich einige von ihnen noch im Prozess der Validierung, aber insgesamt kann der in Abbildung 1dargestellte Ansatz zur neuropsychologischen Diagnostik bei MS als vielversprechend angesehen werden. Wie abgebildet, wird zunächst ein neuropsychologisches Screening durchgeführt, welches grundlegende kognitive Domänen abdeckt und einen Überblick über das Vorliegen kognitiver Beeinträchtigungen gibt. Hierfür empfehlen sich entweder die Kurzform der BRB oder das BICAMS. Im Falle des Vorliegens kognitiver Beeinträchtigungen sollte sich die Durchführung einer ausführlichen Testbatterie zur weiteren Differenzierung dieser Defizite anschließen. Der Aufbau des MACFIMS ist dabei grundsätzlich geeignet, die häufig beeinträchtigten Leistungsbereiche von Aufmerksamkeit, Gedächtnis, Exekutivfunktionen und visuo-räumlichen Funktionen abzudecken und dient als Grundlage der in Abbildung 1 dargestellten Testbatterie. Trotzdem empfehlen sich eine Reihe von Anpassungen: Neben einer eingehenderen Untersuchung von Aufmerksamkeitsleistungen – z.B. mittels der TAP – sollten abhängig von den subjektiven Beschwerdeschilderungen und der spezifischen Fragestellung weitere Testverfahren bei Bedarf integriert werden. Da für alle in der Basis-Testbatterie angegebenen Verfahren Parallelformen vorliegen, ist die Durchführung regelmäßiger Verlaufskontrollen möglich.

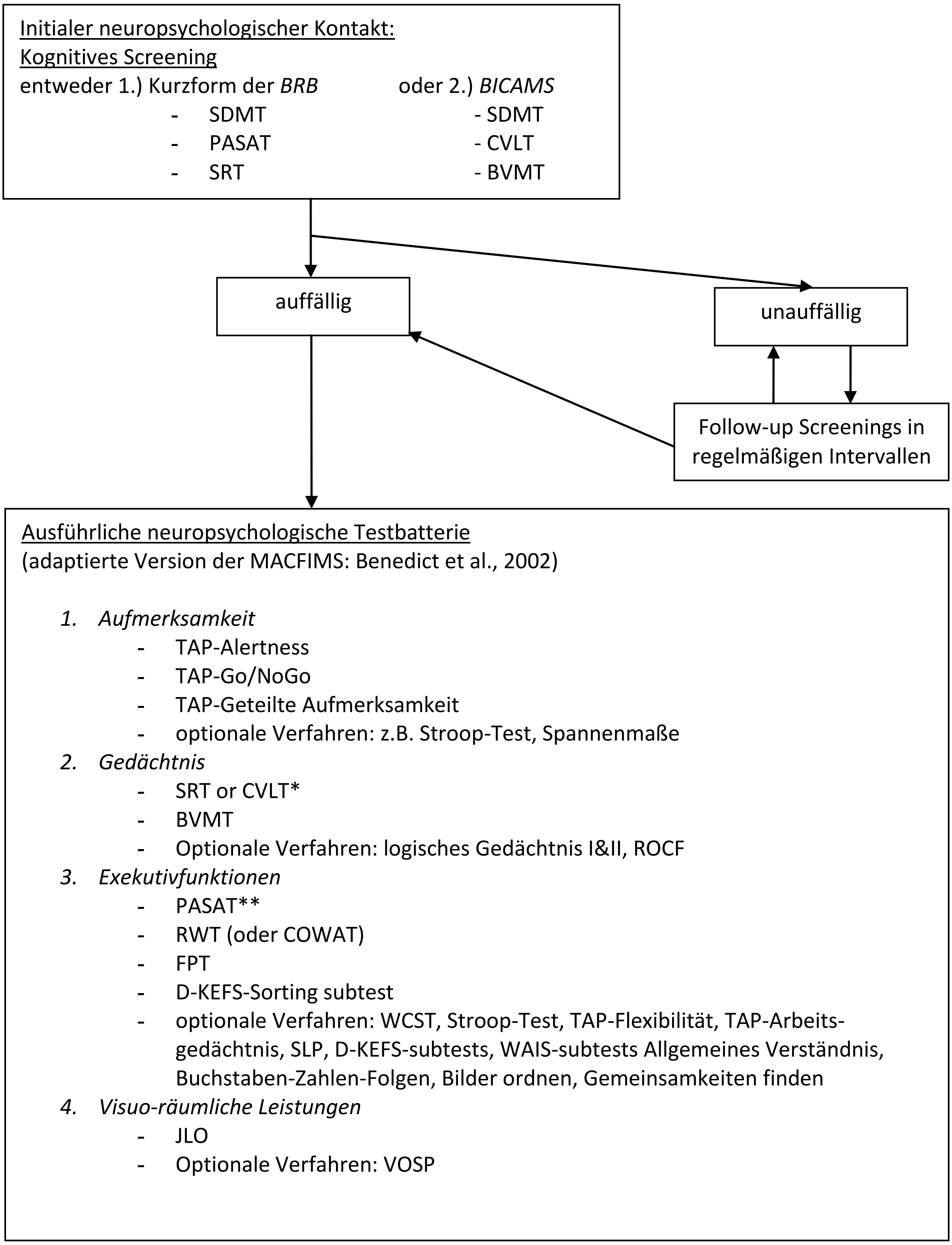

Abbildung 1: Vorschlag für einen neuropsychologischen diagnostischen Algorithmus bei MS-Patienten.

* entweder SRT oder CVLT – abhängig davon, welcher bereits im Screening eingesetzt wurde.

** falls der PASAT noch nicht im Screening eingesetzt wurde.

4.2 Eigene empirische Arbeiten

Unter der wissenschaftlichen Leitung von Professor Stefan Lautenbacher und Dr. Philipp Keune erfolgten an der Klinikum Bayreuth GmbH zwei empirische Studien zur Vorhersagekraft kognitiver Screenings bei MS. In der ersten dieser Studien wurde der prädiktive Wert der bereits vorgestellten Kurzform der BRB untersucht. In der zweiten Studie wurde überprüft, ob der diagnostische Wert der Kurzform der BRB erhalten bleibt, wenn das Screeningverfahrenim Sinne einer größeren diagnostischen Breite und Patientenfreundlichkeit geringfügig modifiziert wird.

Trotz der inhaltlich unterschiedlichen Fragestellungen ergeben sich für beide Studien eine Reihe methodischer Gemeinsamkeiten, die vorab geschildert werden sollen.

4.2.1 Übergreifende Methodik

4.2.1.1 Probanden

In beiden Studien wurden MS-Patienten rekrutiert, die sich in ambulanter oder stationärer neurologischer Behandlung in der Klinik für Neurologie der Klinikum Bayreuth GmbH befanden. Teilnehmende Patienten mussten eine MS-Diagnose nach McDonald-Kriterien (McDonald et al., 2001) aufweisen, sowie zwischen 18 und 75 Jahren alt sein. Ausschlusskriterien waren neben anderen neurologischen Erkrankungen erhebliche visuelle oder motorische Beeinträchtigungen, die eine neuropsychologische Testung unmöglich gemacht hätten. Patienten wurden ebenfalls ausgeschlossen, sofern sie aktuell unter einem Schub litten oder eine Kortisonstoßtherapie erhielten oder innerhalb der letzten vier Wochen erhalten hatten.

4.2.1.2 Kurzform der Brief Repeatable Battery

Wie bereits beschrieben besteht die Kurzform der BRB aus drei Tests, welche hier näher erläutert werden sollen. Die Durchführung der drei Testverfahren allein nimmt etwa 20 Minuten in Anspruch:

Symbol Digit Modalities Test (SDMT): In der von uns angewendeten Variante des SDMT (Smith, 1982) müssen verbale Paarungen von Zahlen und Symbolen vorgenommen werden. Das Schema dieser Paarungen ist dabei vorgegeben und bleibt dem Probanden über den gesamten Testzeitraum von 90 Sekunden einsichtig. Der Outcome-Parameter ist die Anzahl korrekt genannter Paarungen innerhalb der Zeitbegrenzung. Der Test wird als Maß für Aufmerksamkeit und Informationsverarbeitungsgeschwindigkeit angesehen.

*Paced Auditory Serial Addition Test (PASAT):*Beim PASAT (Strauss et al., 2006) werden dem Probanden 61 Zahlen vorgelesen. Es ist die Aufgabe des Probanden, stets die Summe der beiden zuletzt gehörten Zahlen zu nennen. Somit können maximal 60 Punkte bei dieser Aufgabe erzielt werden. Es existieren verschiedene Varianten des PASAT mit variierenden Intervallen zwischen der

Nennung der einzelnen Zahlen. Die von uns verwendete Variante des PASAT verwendet ein Interstimulusintervall (ISI) von 3 Sekunden, was auch im MSFC zur Anwendung kommt. Neben Informationsverarbeitungsgeschwindigkeit erfordert der PASAT vor allem Arbeitsgedächtnisleistung. Diese kann wiederum sowohl als Aufmerksamkeits- als auch als Exekutivfunktion angesehen werden.

*Selective Reminding Test (SRT):*Der SRT (Buschke & Fuld, 1976) ist eine Variante des häufig zum Einsatz kommenden Wortlistenlernens. Zunächst werden dem Probanden zwölf Worte vorgelesen. Es folgt ein direkter freier Abruf. In den weiteren Durchgängen werden jeweils nur die Worte noch einmal vom Testleiter vorgelesen, die im direkt vorhergehenden Durchgang vom Probanden nicht reproduziert wurden. Dieses Vorgehen wird so lange wiederholt, bis der Proband die vollständige Liste zweimal hintereinander wiedergibt, maximal jedoch über sechs Durchgänge. Zwei Parameter können hieraus abgeleitet werden: (1) Es wird angenommen, dass ein Wort den Langzeitspeicher (long-term storage, LTS) erreicht hat, sobald es bei zwei aufeinanderfolgenden Durchgängen genannt wurde. (2) Wenn es daraufhin wieder nicht genannt wurde, wird angenommen, dass der Proband es nicht abrufen konnte. Der Parameter konsistenter Langzeitabruf (consistent long-term retrieval, CLTR) beinhaltet somit alle Wörter, die konsistent über alle Lerndurchgänge bis zum letzten Durchgang abgerufen wurden. Konsequenterweise handelt es sich beim SRT um einen Test zum deklarativen, episodischen Gedächtnis.

4.2.1.3 Der Fünf-Punkt Test

Neben dem etablierten Screening-Verfahren kamen eine Reihe weiterer neuropsychologischer Tests zum Einsatz. In beiden Studien wurde der Fünf-Punkt Test (FPT: Regard et al., 1982) eingesetzt. Der Test erfasst figurale Produktivität und Flexibilität im Sinne frontalhirnassoziierter Exekutivfunktionen. Die Vorlage des FPT besteht aus einem Arbeitsblatt mit 40 gleich großen Quadraten in einer 5x8 Anordnung. In jedem Quadrat befinden sich fünf Punkte, die wie bei der 'Fünf' auf einem Würfel angeordnet sind. Die Aufgabe des Probanden ist es, diese Punkte innerhalb von drei Minuten auf möglichst viele verschiedene Arten zu einem Muster zu verbinden. Sollte der Proband das Ende des Arbeitsblattes erreichen, wird ihm ein neues Arbeitsblatt hingeschoben. Probanden werden instruiert, sich möglichst nicht zu wiederholen. Einer Studie von Goebel, Fischer, Ferstl und Mehdorn (2009) folgend, lassen sich drei Parameter anhand der Leistung des Probanden ermitteln:

Produktivität: Dies ist die Anzahl korrekter produzierter Muster. Alle Repetitionen, Perseverationen oder Regelbrüche werden von der Gesamtzahl produzierter Items abgezogen, um die Produktivität zu ermitteln. Regelbrüche beinhalten das Verbinden von Punkten verschiedener Quadrate, das Zeichnen von Ungeraden Linien oder von Linien, die nicht zwei Punkte miteinander verbinden.

Strategienutzung: Der Strategiescore wird berechnet, indem alle Muster, die durch Rotation oder Spiegelung des vorhergehenden Musters (Rotationsstrategie) oder durch Hinzufügen einer einzelnen zusätzlichen Linie zum vorhergehenden Muster (Additionsstrategie) produziert wurden, summiert und durch den Produktivitätswert dividiert werden.

Wiederholungen: Der Repetitionsscore wird berechnet, indem alle Muster, die eine Wiederholung bereits vorhandener Muster darstellen, zusammengezählt und durch die Gesamtzahl der produzierten Muster dividiert werden.

4.2.1.4 Weitere neuropsychologische Diagnostik

Zusätzlich zum FPT wurde in der ersten Studie eine neuropsychologische Testbatterie als Goldstandard zur Bewertung des Vorliegens kognitiver Defizite durchgeführt, welche aus den folgenden Verfahren bestand und deren Durchführung insgesamt etwa zwei Stunden Zeit beanspruchte:

Testbatterie zur Aufmerksamkeitsprüfung (TAP): Die TAP (Zimmermann & Fimm, 2009) umfasst eine Reihe von computerisierten Untertests zu verschiedenen Aspekten der Aufmerksamkeit. Drei dieser Untertests wurden in der ersten Studie eingesetzt:

Der Subtest ‚*Alertness*' erfasst die psychomotorische Reaktionsgeschwindigkeit des Probanden unter zwei Bedingungen. In der ersten Bedingung muss der Proband auf das Erscheinen eines Kreuzes in der Mitte des Bildschirmes durch raschen Tastendruck reagieren (intrinsische Alertness). In der zweiten Bedingung ertönt ein Warnton vor Erscheinen des Kreuzes. Auch hier soll der Proband möglichst rasch nach Erscheinen des Kreuzes reagieren (phasische Alertness). Outcome-Parameter sind jeweils die Mittleren Reaktionszeiten.

Im Untertest ‚*Go-Nogo*' erscheinen in der Mitte des Bildschirms unregelmäßig entweder ein Kreuz (‚X') oder ein Plus (‚+'). Der Proband muss möglichst rasch bei Erscheinen eines Kreuzes mit Tastendruck reagieren, jedoch nicht bei Erscheinen eines Plus. Der Test erfasst insofern selektive Aufmerksamkeitsleistung im Sinne der Reaktionsinhibition. Outcome-Parameter sind neben der Mittleren Reaktionszeit auch die Anzahl Fehler und Auslassungen.

Zuletzt umfasst der Untertest ‚Geteilte Aufmerksamkeit' zwei simultan ablaufende Prozesse, die gleichzeitig beachtet werden müssen. Erstens erscheint ein sich regelmäßig veränderndes Muster aus Punkten und Kreuzen in der Mitte des Bildschirms, welches auf das Vorliegen einer Anordnung von 2x2 Kreuzen abgesucht werden muss. Zweitens hört der Proband in einem regelmäßigen Intervall abwechselnd hohe und tiefe Töne. Gelegentlich wird dieses Schema durch das Ertönen zweier gleicher Töne direkt hintereinander durchbrochen, worauf ebenfalls reagiert werden soll. Dieser Subtest erfasst die selektive Aufmerksamkeitsleistung im Sinne der Fähigkeit zur Aufmerksamkeitsteilung. Outcome-Parameter sind neben den Mittleren Reaktionszeiten die Anzahl der Fehler und Auslassungen.

California Verbal Learning Test (CVLT): Der CVLT (Niemann et al., 2008) ist ein Test zum Wortlistenlernen. Er beinhaltet 16 Begriffe, die sich vier semantischen Kategorien zuordnen lassen. Die Begriffe werden dem Probanden fünfmal vorgelesen, wobei nach jedem Durchgang ein direkter Abruf erfolgt. Nach dem fünften Lerndurchgang wird eine Distraktorliste vorgelesen und muss ebenfalls direkt abgerufen werden. Ferner erfolgt ein freier Abruf der ersten Liste nach der Distraktorliste und ein verzögerter freier Abruf nach ca. einer halben Stunde. Der Test erfasst insofern das deklarative, episodische Gedächtnis. Von den zahlreichen ableitbaren Parametern fanden nur einige Eingang in die Studie: initiale- und Gesamtlernleistung, Abruf nach Interferenz und nach Verzögerung, Abruf der Distraktorliste.

Wechsler Memory Scale - Zahlenspanne (WMS): Hier werden dem Probanden Zahlenreihen vorgelesen, welche dieser direkt im Anschluss in derselben Reihenfolge wiederholen soll (Härting et al., 2000). Die Reihen werden dabei sukzessive länger. In einer zweiten Bedingung soll der Proband die ihm vorgelesenen Zahlenreihen rückwärts wiederholen. Der Test erfasst insofern in der Vorwärtsbedingung die verbale Merkspanne und in der Rückwärtsbedingung auch Exekutivfunktionsleistung im Sinne des Arbeitsgedächtnis. Outcome-Parameter sind jeweils die Anzahl der korrekt wiedergegebenen Zahlenreihen.

*Wechsler Memory Scale - Blockspanne (WMS):*Dieser Untertest der WMS kann als nonverbales Gegenstück zur Zahlenspanne bezeichnet werden. Der Proband muss eine visuelle Sequenz (Antippen von Blöcken auf einem Testbrett) wiederholen. In der zweiten Bedingung muss die vorgegebene Sequenz rückwärts wiederholt werden. Analog zur Zahlenspanne erfasst dieser Test somit die nonverbale Merkspanne und in der Rückwärtsbedingung wiederum auch Arbeitsgedächtnisleistung.

Regensburger Wortflüssigkeits-Test (RWT): Im RWT (Aschenbrenner, Tucha & Lange, 2000) müssen innerhalb einer Zeitbegrenzung – hier innerhalb einer Minute – möglichst viele Begriffe genannt werden, die ein bestimmtes Zielkriterium erfüllen. Vier Bedingungen werden vorgegeben: Semantische Flüssigkeit (Vorgabe einer Kategorie – Tiere oder Lebensmittel), Phonematische Flüssigkeit (Vorgabe eines Anfangsbuchstabens – M-Wörter oder S-Wörter), Semantische Wechselbedingung (Abwechseln zwischen zwei Zielkategorien – Sportarten und Früchte oder Kleidung und Blumen), Phonematische Wechselbedingung (Abwechseln zwischen zwei Anfangsbuchstaben – G und R oder H und T). Outcome-Parameter sind jeweils die Anzahl der entsprechend der Vorgabe genannten Begriffe. Der Test erfasst neben verbaler Produktivität auch divergentes Denken.

4.2.2 Empirische Studie I

Hansen, S., Münßinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P. & Keune P.M. (2015) Cognitive screening tools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. BMC Neurology, 15 (1),246-253.

4.2.2.1 Theoretischer Hintergrund

Wie bereits erwähnt treten kognitive Beeinträchtigungen bei MS-Patienten häufig auf und stellen eine potentielle Beeinträchtigung der Lebensqualität dar. Da die Erstmanifestation der MS häufig in das Alter der beruflichen und sozialen Etablierung fällt, stellen diese kognitiven Beeinträchtigungen insofern auch ein sozio-ökonomisches Hindernis für die Patienten dar. Darüber hinaus kommt der Diagnostik kognitiver Beeinträchtigungen bei MS eine zusätzliche Bedeutung zu, da diese in einigen Fällen den körperlichen Defiziten vorausgehen und auch als Verlaufsparameter herangezogen werden können.

Trotz der Bedeutung dieser Defizite bleiben sie bei routinemäßigen neurologischen Behandlungen häufig unentdeckt. Dies mag damit zusammenhängen, dass im klinischen Alltag Zeit und Ressourcen häufig eingeschränkt sind, und für die Durchführung einer ausführlichen neuropsychologischen Diagnostik mitunter kein qualifizierter Neuropsychologe zur Verfügung steht. Aus diesem Grunde wurden verschiedene Screeningverfahren entwickelt, die auch von geschulten Praxishelfern angewendet werden können, um mit geringem zeitlichen Aufwand eine Aussage über das Vorliegen oder die Abwesenheit kognitiver Beeinträchtigungen treffen zu können. Eines dieser Screening-Verfahren ist eine Kurzform der Brief Repeatable Battery (BRB), welche bereits vorgestellt wurde. Eine Validierung dieser Kurzform erfolgte bereits vor einigen Jahren (Portaccio et al., 2009) und zeigte sehr vielversprechende Ergebnisse hinsichtlich Sensitivität (94%) und Spezifität (84%) im Vergleich zu einem Goldstandard. Ein erheblicher methodischer Mangel der genannten Studie lässt jedoch Zweifel an der Generalisierbarkeit dieser Ergebnisse aufkommen: Der Goldstandard bestand aus der vollständigen BRB, das Screeningverfahren aus der Kurzform der BRB (SRT, SDMT, PASAT) sowie einem Stroop-Test. Es bestand also eine erhebliche Redundanz von Screeningverfahren und ausführlicher Testung, was die Werte von Sensitivität und Spezifität wahrscheinlich artifiziell erhöhte.

Da wir das Vorgehen, mit der Kurzform der BRB zu screenen, grundsätzlich für sinnvoll erachten, war es das Ziel der ersten empirischen Studie, eine erneute Überprüfung von Sensitivität und Spezifität dieser Kurzform vorzunehmen. Dabei wurde gewährleistet, dass bei der Überprüfung der prognostischen Validität des Screenings anhand des Goldstandards einer ausführlichen neuropsychologischen Testung beide Verfahren unabhängig voneinander waren.

4.2.2.2 Methode

126 Patienten (weiblich: 66,9%) mit MS oder klinisch wahrscheinlicher MS wurden für die erste Studie rekrutiert (Alter: M = 42,9 Jahre, SD = 11,0). Die durchschnittliche Erkrankungsdauer betrug 9,5 Jahre (SD: 9,2). Die Patienten erhielten zwei Untersuchungstermine: Bei dem ersten Termin wurde das kognitive Screening durchgeführt, bei dem zweiten Termin die ausführliche neuropsychologische Diagnostik. Eine Beschreibung hierzu findet sich jeweils im Abschnitt zur übergreifenden Methodik. Zwischen Screening und ausführlicher Testung vergingen durchschnittlich 4,2 Monate (SD = 4,2 Monate), maximal jedoch ein Jahr. Als kognitiv auffällig im Screening galt, wer in mindestens einem der angegebenen Testparameter ein Ergebnis unterhalb PR 16 oder einer Standardabweichung (SD) unter dem Mittelwert aufwies. Dasselbe Kriterium wurde mit einer Ausnahme auch für die ausführliche Testdiagnostik angewendet: Da der CVLT vergleichsweise viele Parameter beinhaltete, galt hier als auffällig, wer bei mindestens zwei Parametern schlechter als eine SD unter dem Mittelwert abschnitt.

4.2.2.3 Ergebnisse

In der ersten empirischen Studie zeigten 72 Patienten (57,1%) ein auffälliges Ergebnis in der ausführlichen Testung, wohingegen 75 Patienten (59,5%) ein auffälliges Ergebnis im Screening aufwiesen. Für die Kurzform der BRB ergaben sich im Vergleich zum Goldstandard einer ausführlichen Testbatterie ein Sensitivitätswert von 77,8% und ein Spezifitätswert von 64,8%. Die entsprechende Vierfeldertafel kann in Tabelle 1konsultiert werden.

Tabelle 1: Kreuztabelle mit den Angaben der diagnostischen Kongruenz von ausführlicher neuropsychologischer Testung und kognitivem Screening

		Ausführliche Testung		
		Kognitiv beeinträchtigt	Kognitiv unbeeinträchtigt	
Screening	Kognitiv beeinträchtigt	N = 56 Sensitivität = 77,78%	N = 19	N = 75
	Kognitiv unbeeinträchtigt	N = 16	N = 35 Spezifität = 64,81%	N = 51
		N = 72	N = 54	

Darüber hinaus wurden die Werte für Sensitivität und Spezifität auch jeweils für die einzelnen Untertests des Screenings berechnet. Dabei ergaben sich für den SRT (Sensitivität: 38,4%; Spezifität: 81,5%), SDMT (Sensitivität: 43,8%, Spezifität: 94,4%) und PASAT (Sensitivität: 41,7%, Spezifität: 87%) jeweils ausgesprochen mäßige Werte bezüglich Sensitivität, hingegen jedoch zum Teil sehr hohe Werte bezüglich Spezifität.

Zuletzt wurden auch Sensitivität und Spezifität der einzelnen Untertests des Screenings in Bezug auf die Ergebnisse der Tests aus dem Goldstandard untersucht, welche die gleiche kognitive Domäne erfassen. Dabei wurden sämtliche TAP-Parameter und der SDMT der Domäne Aufmerksamkeit zugeordnet. Der SDMT erreichte dabei eine Sensitivität von 52,9% und eine Spezifität von 89,5%. Der SRT und sämtliche CVLT-Parameter wurden der Domäne Gedächtnis zugeordnet, wobei der SRT eine Sensitivität von 60% und eine Spezifität von 81,5% erreichte. Die übrigen Parameter der ausführlichen Testung (FPT, RWT, WMS) wurden ebenso wie der PASAT der Domäne der Exekutivfunktionen zugewiesen. In Hinblick auf die Tests des Goldstandards aus dieser Domäne erreichte der PASAT eine Sensitivität von 49,1% und eine Spezifität von 84,9%.

4.2.2.4 Diskussion

In der aktuellen Studie erreichte die Kurzform der BRB hinreichende Werte von Sensitivität (77,8%) und Spezifität (64,8%). Zwar liegen diese Ergebnisse deutlich unter denen der Studie von Portaccio et al. (2009), doch aufgrund der Tatsache, dass bei der aktuellen Studie ein Vergleich mit den Ergebnissen einer unabhängigen Testbatterie als Goldstandard vorgenommen wurde, dürften unsere Ergebnisse den tatsächlichen prädiktiven Wert der Kurzform der BRB realistischer abbilden. Außerdem ist darauf hinzuweisen, dass auch das recht lange Intervall zwischen Screening und ausführlicher Testung sich möglicherweise negativ auf Sensitivität und Spezifität ausgewirkt haben könnte. Trotz dieses etwas ernüchternden Ergebnisses kann die Kurzform der BRB jedoch als Screening-Instrument empfohlen werden.

Weiterhin zeigte sich, dass nur die Kombination der drei Testverfahren eine hinreichend hohe Sensitivität ergab, um als Screening-Verfahren sinnvoll eingesetzt werden zu können. Im Gegensatz zu Vorschlägen anderer Autoren (Sonder et al., 2013), einzig auf den SDMT als Screening-Instrument zu setzen, postulieren wir weiterhin den Einsatz der vollständigen Kurzform der BRB, da die Spezifität des SDMT zwar ausgesprochen hoch war, die Sensitivität jedoch kaum oberhalb der

Ratewahrscheinlichkeit lag. Da ein kognitives Screening im Sinne einer sicheren Diagnosestellung jedoch eher zu konservativ als zu liberal sein sollte, ist eine niedrige Sensitivität – also die Wahrscheinlichkeit, einen Fehler erster Ordnung zu begehen –besonders zu vermeiden.

4.2.3 Empirische Studie II

Hansen, S., Münßinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P. & Keune, P.M. (2017) Cognitive screening in multiple sclerosis: the Five-Point-Test as a substitute for the PASAT in measuring executive function. The Clinical Neuropsychologist, 31 (1), 179-192.

4.2.3.1 Theoretischer Hintergrund

In der ersten empirischen Studie hatte sich die Kurzform der BRB als hinreichend sensitiv und spezifisch in Bezug auf einen Goldstandard erwiesen. Neben der Kurzform der BRB existiert mit dem Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS: Langdon et al, 2012) noch ein weiteres etabliertes Screening-Verfahren, welches hinreichende Werte von Sensitivität und Spezifität in Bezug auf einen Goldstandard erreicht (Dusankova, Kalincik, Havrdova & Benedict, 2012). Die BRB wird von uns jedoch favorisiert, da sie im Gegensatz zum BICAMS mit dem PASAT einen Untertest beinhaltet, der auch die bei MS-Patienten häufig betroffene Domäne der Exekutivfunktionen erfasst. Allerdings liegt im PASAT auch ein Schwachpunkt der BRB begründet: So wurde ausgeführt, dass der PASAT als Screeninginstrument möglicherweise ungeeignet ist, da er neben grundlegenden kognitiven Funktionen wie Informationsverarbeitungsgeschwindigkeit (Forn, Belenguer, Parcet-Ivars & Avila, 2008) und Arbeitsgedächtnis (Rogers & Panegyres, 2007) auch eher begabungsabhängige Leistungen wie grundlegende arithmetische Fähigkeiten und Rechengeschwindigkeit erfordert (Sandry, Paxton & Sumowski, 2016). Darüber hinaus wird der PASAT unabhängig von der kognitiven Leistungsfähigkeit häufig als unangenehm und fordernd erlebt (Fisk & Archibald, 2001), was bei einigen Patienten zu Reaktanz und Teilnahmeverweigerung führt. Einige Autoren schlugen aus diesen Gründen vor, den PASAT ersatzlos zu streichen und sich stattdessen auf den SDMT als Screeninginstrument zu beschränken (Sonder et al., 2013). Allerdings ist der prädiktive Wert des SDMT allein – wie in Studie I dargestellt – keineswegs hinreichend, um als alleiniger Prädiktor kognitiver Beeinträchtigungen zu fungieren.

Insofern stellt sich die Frage, ob der PASAT durch ein Verfahren ersetzt werden könnte, welches sich auf die Erfassung grundlegender kognitiver Funktionen beschränkt und von Patienten unvoreingenommen bearbeitet werden kann. Als solches Verfahren erscheint der FPT naheliegend, der im allgemeinen Methodenteil bereits näher erläutert wurde. Die Bearbeitungszeit beträgt genau wie beim PASAT drei Minuten, was ihn als Screeningverfahren prädestiniert, und dank der etablierten Normen zu Strategienutzung bei der Itemgeneration (Goebel et al., 2009; Goebel, Atanassov, Köhnken, Mehdorn & Leplow, 2013) erfasst er neben psychomotorischer Geschwindigkeit und nonverbaler Produktivität auch Exekutivfunktionen im Sinne strategischen Vorgehens bei der Aufgabenbearbeitung.

Ziel der zweiten empirischen Studie ist es daher zu evaluieren, ob der FPT ein geeigneter Ersatz für den PASAT in der Kurzform der BRB als kognitives Screening sein könnte.

4.2.3.2 Methode

Für die zweite empirische Studie wurden 116 Patienten (weiblich: 66,4%) mit diagnostizierter MS rekrutiert (Alter: M = 42,8, SD = 11,5). Die durchschnittliche Erkrankungsdauer betrug 10,5 Jahre (SD = 8,5 Jahre). Die Patienten befanden sich zum Zeitpunkt der Untersuchung entweder in ambulanter oder stationärer Behandlung. Das neuropsychologische Screening mit der Kurzform der BRB sowie der FPT wurden während eines neuropsychologischen Untersuchungstermins im Rahmen der klinischen Routine durchgeführt. Beide Verfahren wurden im allgemeinen Methodenteil bereits detailliert dargestellt. Analog zu Studie I galten jene Patienten als kognitiv beeinträchtigt, die in einem oder mehreren der Untertests ein Ergebnis erreichten, welches mehr als eine SD unter dem Mittelwert lag.

4.2.3.3 Ergebnisse

Eine deskriptive Korrelationsanalyse der Testparameter zeigte unter anderem hoch signifikante Korrelationen ($p < .01$) zwischen dem PASAT und dem SDMT, sowie dem PASAT und den beiden FPT-Parametern Produktivität und Strategienutzung. Zur weiteren Analyse des Zusammenhangs zwischen PASAT und FPT wurde eine Faktoranalyse mit Promax-Rotation unter Einbezug aller erfassten Variablen durchgeführt, um die zugrundeliegende Faktorstruktur zu untersuchen. Diese beinhaltete sämtliche erhobenen z-transformierten Testparameter. Der Bartlett-Test erwies sich als hoch signifikant und das Kaiser-Meyer-Olkin—Kriterium erreichte einen Wert von .709, was als adäquat gilt. Beide Ergebnisse sprechen dafür, dass die vorliegenden Daten für die Durchführung einer Faktorenanalyse geeignet sind. Zwei Faktoren mit Eigenwerten >1 klärten 67,02% der Varianz auf (Faktor 1: 45,39%, Faktor 2: 21,63%). Auf dem ersten Faktor luden der PASAT, SDMT, sowie die FPT-Parameter Produktivität und Strategienutzung. Auf dem zweiten Faktor luden die SRT-Parameter LTS und CLTR.

Zuletzt wurden die Ergebnisse beider Screenings verglichen. Dies kann anhand der in Tabelle 2 dargestellten Vierfeldertafel nachvollzogen werden. Während in der ursprünglichen Kurzform der BRB 69 Patienten (59,5%) als kognitiv beeinträchtigt identifiziert wurden, identifizierte die alternative Version des Screenings, in welcher der PASAT durch den FPT ersetzt wurde, 73 Patienten (62,9%) als kognitiv beeinträchtigt. Die Kongruenz bzgl. der Gruppe der kognitiv beeinträchtigten Patienten betrug 89,9%, die Kongruenz bzgl. der unbeeinträchtigten Patienten lag bei 76,6%.

Abbildung 2: Kreuztabelle mit Angaben zur diagnostischen Kongruenz des klassischen Screeningansatzes (Kurzform der BRB) und der adaptierten Version, in welcher der FPT den PASAT ersetzt.

		SDMT + SRT-LTS + SRT-CLTR + FPT-Produktivität + FPT-Strategienutzung		
		Kognitiv beeinträchtigt	Kognitiv unbeeinträchtigt	
SDMT + SRT-LTS+ SRT-CLTR + PASAT	Kognitiv beeinträchtigt	N = 62 Kongruenz = 89,9%	N = 7	N = 69
	Kognitiv unbeeinträchtigt	N = 11	N = 36 Kongruenz = 76,6%	N = 47
		N = 73	N = 43	

4.2.3.4 Diskussion

Die zweite empirische Studie konnte entsprechend unserer Erwartungen überzeugende Hinweise dafür liefern, dass PASAT und FPT eine große inhaltliche Redundanz bezüglich der von ihnen erfassten neuropsychologischen Leistungen besitzen. Dies zeigte sich zunächst in der Korrelationsanalyse, in welcher der PASAT mit zwei der drei FPT-Parameter hoch signifikant korrelierte. Weiterhin luden beide Parameter in einer Faktorenanalyse auf demselben Faktor. Zuletzt erbrachten beide Verfahren in Kombination mit SRT und SDMT vergleichbare Ergebnisse bei der Prädiktion kognitiver Beeinträchtigungen. Aus unserer Sicht scheinen diese Ergebnisse plausibel, da beide Verfahren einen Schwerpunkt auf der Erfassung von Exekutivfunktionen legen, obwohl der PASAT eher Arbeitsgedächtnisleistung erfordert, und der FPT als Maß für nonverbale Produktivität angesehen werden sollte. Daneben liegt bei beiden Testverfahren eine Konfundierung mit Informationsverarbeitungsgeschwindigkeit vor, was sich in der zweiten empirischen Studie anhand der Tatsache zeigt, dass auch der SDMT als Maß für Informationsverarbeitungsgeschwindigkeit auf demselben Faktor lädt wie PASAT und FPT. Insofern erscheint der FPT dem PASAT hinsichtlich seines prädiktiven Wertes zumindest ebenbürtig zu sein.

Möglicherweise ist der FPT dem PASAT als Bestandteil der Kurzform der BRB sogar überlegen. Erstens ergibt sich – anders als beim PASAT – die Möglichkeit, mehrere Parameter zu ermitteln anhand derer die einzelnen Beiträge der kognitiven Domänen zur Testleistung aufgeschlüsselt werden können (Anzahl produzierter Items, Strategienutzung, Repetitionen). Zweitens ist der FPT nicht mit arithmetischen Fähigkeiten konfundiert. Drittens ist uns nicht bekannt, dass der FPT bei Patienten eine vergleichbare Abwehrreaktion auslöst wie der PASAT.

Einschränkend ist zu erwähnen, dass der PASAT aufgrund der motorischen Anforderungen für Patienten mit einem hohen EDSS (Expanded Disability Status Scale: Kurtzke, 1983) seinen prädiktiven Wert verliert. Weiterhin sollten die aktuellen Ergebnisse hinsichtlich der prädiktiven Kongruenz der beiden alternativen Verfahren nicht als Sensitivität und Spezifität aufgefasst werden, da hierfür der Abgleich anhand der Ergebnisse eines Goldstandards erforderlich wäre.

Trotz dieser Einschränkungen sprechen die Ergebnisse der zweiten empirischen Studie jedoch grundsätzlich dafür, dass der FPT eine sinnvolle Alternative zum PASAT in einem kognitiven Screening darstellen könnte.

5. Übergreifende Diskussion

Ziel dieser Dissertation war es, einen Überblick über die Möglichkeiten neuropsychologischer Diagnostik bei MS zu geben und den Leser über Vor- und Nachteile verschiedener diagnostischer Verfahren zu informieren. Anhand der so erbrachten Übersichtsarbeit wurde ein Prozedere vorgeschlagen, welches sich als Schema zur neuropsychologischen Diagnostik heranziehen lässt, und trotzdem modifizier- und erweiterbar bleibt.

Einige der in diesem Prozedere implementierten neuropsychologischen Testverfahren (Kurzform der BRB) kommen zwar seit geraumer Zeit in unterschiedlicher Form in der neuropsychologischen Diagnostik bei MS vor, wurden jedoch bis dato nicht hinreichend validiert. Der zweite Teil dieser Dissertation beschäftigte sich folglich mit der Validierung der Kurzform der BRB und erbrachte Ergebnisse, welche für die grundsätzliche Einsetzbarkeit der Kurzform der BRB als neuropsychologisches Screening bei MS sprechen.

Zuletzt wurde die Möglichkeit untersucht, die bestehende Kurzform der BRB zu modifizieren, indem der PASAT gegen den FPT ausgetauscht wurde. Die Notwendigkeit hierzu ergab sich aufgrund anhaltender Kritik am PASAT sowohl von Seiten der Diagnostiker als auch von Seiten der Patienten. Die Ergebnisse dieser ersten Studie sprechen auch hier dafür, dass der prognostische Wert des Screenings durch diese Modifikation nicht grundlegend beeinträchtigt wird.

Die folgende übergreifende Diskussion soll die erbrachten Ergebnisse nun in den Kontext des aktuellen Forschungsstandes eingruppieren und kritisch würdigen.

5.1 Vorschlag für eine neuropsychologische Testbatterie bei MS

Bereits frühere Studien haben sich mit der Konstruktion einer Testbatterie für MS-Patienten beschäftigt. Besonders hervorzuheben sind Bestrebungen von Rao (1990), Franklin, Heaton, Nelson, Filley und Seibert (1988) und in jüngeren Jahren Benedict et al. (2002). Diesen Ansätzen ist zueigen, dass als Grundlage der Konstruktion der Testbatterie rein theoretische Überlegungen standen. Im Gegensatz dazu wurde bei Benedict et al. (2002) eine Expertenkommission befragt, welche Tests bei MS für einzelne Teilleistungsbereiche als besonders sinnvoll zur Beurteilung der kognitiven Leistungsfähigkeit anzusehen seien. Anhand der Vorschläge dieser Expertenkommission wurde das MACFIMS konstruiert. Ein derartiges Vorgehen, ein diagnostisches Procedere gewissermaßen als Produkt der geballten klinischen Erfahrung einer Reihe von Experten zutage zu fördern, kann sicherlich als Ausgangspunkt einer praxisnahen Konstruktion einer Testbatterie als sinnvoll angesehen werden. Allerdings erscheint es verwunderlich, dass in der Folge kaum Bestrebungen unternommen wurden, diese Testbatterie eingehend zu validieren, sondern deren Rolle als

Goldstandard bei der Diagnostik kognitiver Defizite bei MS weitgehend unreflektiert übernommen wurde. Zwar gehen selbst die Initiatoren des MACFIMS auf die Notwendigkeit einer eingehenden Validierung ihrer Testbatterie ein, es finden sich jedoch nur sehr wenige Studien, die zu dieser Validierung beitragen (z.B. Benedict et al., 2006; Dusankova et al., 2012). Insofern kann die im Rahmen dieser Dissertation entstandene Übersichtsarbeit auch als Ansatz aufgefasst werden, um diese theoretische Lücke zu schließen. Zwar wurden keine statistischen Verfahren eingesetzt, um die Verfahren des MACFIMS zu validieren, und es wurde auch keine Übersichtsarbeit im Sinne einer Metaanalyse durchgeführt, aber es wurden relevante Forschungs- und Übersichtsarbeiten zum Thema Diagnostik bei MS gesichtet und bezüglich Studiendaten zu neuropsychologischen Testverfahren untersucht. Dabei wurden sowohl solche Studien berücksichtigt, die Zusammenhänge zwischen bildgebenden Verfahren und neuropsychologischer Diagnostik untersuchten, als auch solche, die Vergleiche zwischen MS-Patienten und gesunden Kontrollen durchführten. So ergab sich ein umfassender Überblick, der ein Abwägen der Vor- und Nachteile verschiedener Testverfahren für verschiedene kognitive Domänen ermöglicht. Hierdurch wird es möglich, die Entscheidung für eine spezifische Testbatterie wie zum Beispiel dem MACFIMS nachzuvollziehen oder gegebenenfalls zu verwerfen.

Die Ergebnisse der Übersichtsarbeit können dabei folgendermaßen interpretiert werden: Grundsätzlich kann die Konstruktion des MACFIMS anhand theoretischer Überlegungen nachvollzogen werden. Bei vielen der im MACFIMS eingesetzten Verfahren erbrachte unsere Literaturrecherche, dass sie vergleichbaren Verfahren, die eine ähnliche kognitive Domäne erfassen, tatsächlich zumindest im Rahmen der MS überlegen sind. Dies betrifft insbesondere die Bereiche Aufmerksamkeit (SDMT) und Arbeitsgedächtnis (PASAT), sowie nonverbale Neugedächtnisleistungen (BVMT). Insbesondere zum Bereich Aufmerksamkeit wäre jedoch anzumerken, dass wir aufgrund der alleinigen Repräsentation durch den SDMT davon ausgehen, dass die Breite dieses Konstruktes nicht ausreichend abgedeckt wird. Darüber hinaus ergaben sich Hinweise, dass einige der zur Verfügung stehenden Alternativen den eingesetzten Verfahren zumindest ebenbürtig sind. Hierunter sind der CVLT zu zählen, der mit dem SRT ein Pendant von mutmaßlich gleichwertigem Prädiktionswert besitzt, sowie eine Aufgabe zur verbalen Produktivität (Word List Generation: WLG), welche zum Beispiel mit dem Regensburger Wortflüssigkeitstest (Aschenbrenner et al., 2000) vergleichbar sein dürfte. Exekutivfunktionen, welche abgesehen vom PASAT nur mit einem weiteren Test im MACFIMS repräsentiert waren, halten wir demgegenüber für nur unzureichend abgebildet. Mehr noch ist das hierfür eingesetzte Verfahren, eine Adaption des Wisconsin Card Sorting Tests (WCST: Heaton, Chellune, Curtiss, Kay & Talley, 1993), bisher nur unzureichend im MS-Kontext validiert.

Aufgrund der Ergebnisse unserer Übersichtsarbeit schlagen wir daher eine Reihe von Modifikationen auf Grundlage des MACFIMS vor, welche anhand von Abbildung 1 nachvollzogen werden können. Der Bereich Aufmerksamkeit sollte zusätzlich durch computergestützte Verfahren erfasst werden, welche über mehrere Untertests verfügen, um verschiedene Teilleistungsbereiche abzudecken (Alertness, selektive Aufmerksamkeit, Orienting). Im Rahmen der neuropsychologischen Diagnostik bei MS hat sich hierfür insbesondere im deutschsprachigen Raum die TAP etabliert. Im Bereich Gedächtnis empfiehlt sich analog zur Durchführung des CVLT auch die Durchführung des SRT. Dieser ist dem CVLT wie bereits erwähnt hinsichtlich prädiktivem Wert vermutlich ebenbürtig, erfasst jedoch aufgrund der Unterschiede in der Präsentation auch unterschiedliche Aspekte der verbalen Neugedächtnisleistung. Zuletzt sollten die Bereiche Exekutivfunktionen und visuo-perzeptive Leistungen je nach Bedarf und abhängig von der spezifischen Fragestellung durch weitere Verfahren ergänzt werden. Dabei empfiehlt es sich, bei der Testung von Exekutivfunktionen bei MS-Patienten auf Verfahren ohne Speed-Komponente zurückzugreifen, da ansonsten die Gefahr besteht, dass es zu einer Konfundierung mit Beeinträchtigungen im Bereich der Informationsverarbeitungsgeschwindigkeit kommt.

Durch die im Rahmen dieser Dissertation durchgeführte Übersichtsarbeit können die begründeten Bedenken hinsichtlich der Validität des MACFIMS zwar nicht zerschlagen werden. Allerdings zeichnet sich ab, dass nicht nur die Befragung einer Expertenkommission, sondern auch eine ausführliche Literaturrecherche hinsichtlich der zu empfehlenden Diagnostik bei MS in vielen Bereichen zu ähnlichen Ergebnissen kommt. Dort, wo diese Ergebnisse nicht übereinstimmen, wurden Verbesserungsvorschläge anführt.

5.2 Die Kurzform der BRB als neuropsychologisches Screening bei MS

Wie bereits erwähnt, ist aufgrund der zeitlichen und ökonomischen Gegebenheiten eine ausführliche neuropsychologische Diagnostik bei MS nicht immer möglich. Die aus diesem Grunde entwickelten Screeningverfahren dienen folglich als *Case-Finding Tools*, also zur Bestimmung des kognitiven Status, von deren Ausgang das weitere diagnostische Vorgehen abhängig gemacht wird. Wie aus der hier vorgestellten Übersichtsarbeit hervorgeht, haben sich in den letzten Jahren zwei Screening-Verfahren etabliert (Kurzform der BRB und BICAMS). Beide beinhalten den SDMT, der als sogenannter ‚schmutziger' Test (Hoffmann, Tittgemeyer & von Cramon, 2008) bei MS einen mutmaßlich besonders hohen prädiktiven Wert besitzt, da er zur erfolgreichen Bearbeitung auf die bei MS häufig beeinträchtigte kortikale Interkonnektivität zurückgreift. Beide beinhalten Tests zum verbalen Neugedächtnis (SRT bzw. CVLT), deren prädiktiver Wert als vergleichbar angesehen werden kann. Die Kurzform der BRB enthält zusätzlich den PASAT, der sowohl Exekutivfunktionen im Sinne von Arbeitsgedächtnisleistungen als auch Informationsverarbeitungsgeschwindigkeit erfordert und ebenfalls als ‚schmutziger' Test aufgefasst werden kann. Demgegenüber enthält das BICAMS noch den BVMT, einen Test zum nonverbalen Neugedächtnis. Aufgrund der Tatsache, dass auch Exekutivfunktionen häufig bei MS beeinträchtigt sind, sollten diese unserer Meinung nach auch in einem kognitiven Screening repräsentiert sein, so dass wir die Kurzform der BRB als Screeninginstrument favorisieren. Die wenigen vorliegenden Studien, die sich mit der Frage der prognostischen Validität dieser Instrumente beschäftigen, weisen jedoch für beide vergleichbare, hohe Werte für Sensitivität und Spezifität auf (Portaccio et al., 2009; Dusankova et al., 2012), so dass sich hieraus folglich keine zwingende Notwendigkeit ergibt, eines der Screenings zu präferieren. Beide genannten Studien leiden allerdings unter demselben methodischen Mangel: Beide ziehen als Goldstandard für die Definition kognitiver Beeinträchtigung die Ergebnisse von Tests hinzu, welche ebenfalls Bestandteil des jeweiligen Screenings waren, was zu einer artifiziellen Erhöhung der prognostischen Validität führt.

Unsere Überprüfung der Vorhersagekraft der Kurzform der BRB anhand eines unabhängigen Goldstandards erbrachte zufriedenstellende Werte, die jedoch deutlich unter denen der zuvor von Portaccio et al. (2009) erbrachten Ergebnisse bezüglich Sensitivität und Spezifität lagen. Insofern ist die Frage berechtigt, ob der in der Übersichtsarbeit aufgezeigte Weg, die Entscheidung über die Durchführung einer ausführlichen Testung vom Ergebnis des kognitiven Screenings abhängig zu machen, ein Irrweg sein könnte. Allerdings ist darauf hinzuweisen, dass mit einer Sensitivität von knapp 80% zumindest Fehler 1. Ordnung relativ selten auftreten. Die etwas niedrige Spezifität von knapp 65% kann demgegenüber als vertretbar angesehen werden, da falsch positive Bewertungen sich spätestens bei der Durchführung einer ausführlichen Testung relativieren sollten.

Für eine abschließende Bewertung der Vor- und Nachteile beider Screenings fehlt nun auch eine Studie der prognostischen Validität des BICAMS ermittelt an einem unabhängigen Goldstandard. Ohne diese Daten lässt sich eine realistische Beurteilung darüber, welches Screening-Verfahren zu bevorzugen wäre, nicht oder eben nur anhand persönlicher Präferenzen wie der genannten zusätzlichen Abdeckung von Exekutivfunktionen in der Kurzform der BRB treffen.

5.3 Adaption der Kurzform der BRB

Obwohl die Kurzform der BRB aufgrund der größeren Breite an erfassten kognitiven Domänen präferiert werden kann, sind die in den letzten Jahren gehäuft auftretenden Argumente, die gegen den PASAT sprechen, nicht von der Hand zu weisen. Dabei sollte die Kritik an der inhaltlichen Validität des PASAT nicht überbewertet werden. Abgesehen davon, dass die Leistung im PASAT mit arithmetischen Fähigkeiten konfundiert ist, stellt der Umstand, dass er mit Arbeitsgedächtnis, Informationsverarbeitungsgeschwindigkeit und geteilten Aufmerksamkeitsleistungen gleich mehrere grundlegende kognitive Funktionen erfordert, keinen Grund dar, ihn nicht als Screeninginstrument einzusetzen. Im Gegenteil stellt gerade diese Eigenschaft eines ‚schmutzigen' Tests einen Vorteil für ein *Case-Finding Tool* dar, wie bereits weiter oben in Bezug auf Hoffmann et al. (2008) dargestellt. Allerdings sollte zusätzlich bedacht werden, dass man als Diagnostiker auch auf die Mitarbeit der Patienten angewiesen ist, und idealerweise für eine konzentrierte, angenehme Arbeitsatmosphäre sorgt. Hier stellt der PASAT ein Hindernis dar, denn er wird von vielen Patienten als ausgesprochen unangenehm erlebt. Zum einen liegt dies sicher an der hohen Speed-Komponente des Tests. Zum anderen zeigt die klinische Erfahrung, dass viele Patienten sich überfordert und nachgerade als dumm abgestempelt fühlen, wenn sie die Aufgabe nicht bewältigen können, und bei fortlaufender Präsentation nicht mehr in die Aufgabe hineinfinden. Die Folge sind nicht nur vermindert interpretierbare Testergebnisse, sondern auch eine potentielle Verminderung der Compliance. Ein erfahrener Diagnostiker kann diese Effekte durch bedachte Instruktion abmildern, aber dies wird nicht bei allen Patienten gelingen und so wird immer wieder die Situation eintreten, dass mit Widerständen im Rahmen der neuropsychologischen Untersuchung zu rechnen ist.

Da weder auf einen ‚schmutzigen' Test als *Case-Finding Tool*, noch auf einen Test zur Erfassung der Exekutivfunktionen im Screening verzichtet werden sollte, stellt der FPT eine sinnvolle Alternative dar. Die Eigenschaften des Tests und die ermittelbaren Parameter wurden bereits im Methodenteil erläutert, aber die eindrücklichsten Parallelen zum PASAT sollen hier noch einmal erwähnt werden. Ebenso wie beim PASAT beträgt die Bearbeitungszeit drei Minuten und ebenso wie der PASAT erfordert der FPT mehrere Komponenten kognitiver Leistungsfähigkeit: Psychomotorische Geschwindigkeit sowie Exekutivfunktionen im Sinne von kognitiver Flexibilität und nonverbaler Produktivität. Ein wichtiger Unterschied besteht in der Akzeptanz des Testverfahrens bei den Patienten. Der FPT kam in beiden empirischen Studien zum Einsatz, und bei allen Studienteilnehmern zeigte sich eine breite Akzeptanz. Im Gegensatz zum PASAT musste nicht ein einziger Datensatz aus der Analyse entfernt werden, weil FPT-Daten gefehlt hätten.

Die Ergebnisse der zweiten empirischen Studie sprechen ebenfalls dafür, dass der Einsatz des FPT anstelle des PASAT in der Kurzform der BRB ein gangbarer Weg sein könnte, um ein kognitives Screening mit hohem prädiktivem Wert zu behalten, welches gleichzeitig patientenfreundlich ist. Es muss jedoch berücksichtigt werden, dass der FPT im Gegensatz zum PASAT ein Mindestmaß an feinmotorischen Fähigkeiten erfordert. Diese sind bei MS-Patienten mit fortschreitender Erkrankungsdauer häufig beeinträchtigt, und es stellt sich die Frage, bis zu welchem Punkt eine Bearbeitung der Aufgabe möglich ist, ohne durch die feinmotorische Beeinträchtigung einen Zeitverlust zu erleiden. In der fraglichen Studie wurde als Ausschlusskriterium definiert, dass keine erheblichen Beeinträchtigungen der Feinmotorik vorliegen dürften. In der Praxis ließe sich dies zum Beispiel anhand des EDSS grob ermitteln. Eine genauere Erhebungsmethode – die ebenfalls nur wenig Zeit in Anspruch nehmen würde – wäre die Beurteilung feinmotorischer Fertigkeiten anhand einer Steckbrettaufgabe wie dem Nine-hole peg test (Goodkin, Heertsgard & Seminary, 1988). Eine ähnliche Steckbrettaufgabe ist ebenfalls Bestandteil des MSFC.

Eine kritische Anmerkung zur zweiten empirischen Studie lautete, dass für die Bearbeitung des FPT auch visuo-räumliche Wahrnehmung eine Rolle spielen, und dass visuo-räumliche Beeinträchtigungen zu einer Konfundierung der Ergebnisse beitragen könnten. Wie bereits im Theorieteil erläutert, sind visuo-räumliche Wahrnehmungsstörungen jedoch vermutlich erheblich seltener bei MS anzutreffen, als von manchen älteren Studien postuliert. In der Tat erfordert der FPT, dass der Patient sehen kann, wobei kleinere Beeinträchtigungen der Sehfähigkeit bei der Bearbeitung kompensierbar sein dürften. Insgesamt kann davon ausgegangen werden, dass für die Bearbeitung des FPT ein vergleichbares Maß an Sehfähigkeit vorliegen sollte wie für den SDMT.

5.4 Der besondere Diagnoseweg bei MS: Eine kritische Würdigung

Wie bereits im theoretischen Teil erläutert, kommt der neuropsychologischen Diagnostik bei MS eine gewisse Sonderrolle zu. Zwar sind die verwendeten Verfahren auch für den Einsatz bei anderen Störungsbildern kompatibel, aber zumindest der zweischrittige Diagnoseweg hat sich bei anderen Störungsbildern nicht in dieser Form etabliert. Auch wenn die Gründe für diese Zweiteilung in Screening und ausführliche Testung im Rahmen der klinischen Routine vornehmlich ökonomischer Natur sein mögen, lassen sich auch auf theoretischer Ebene gute Argumente für dieses Vorgehen finden. Eine Erläuterung der Sinnhaftigkeit dieses Dualismus findet sich bereits in Abschnitt 2.5 und besteht aus dem Versuch einer Erklärung, weswegen MS einerseits eine interindividuell sehr variable Erkrankung sein kann, der aber gleichzeitig möglicherweise doch ein gemeinsames kognitives Kardinalsymptom zugrundeliegt.

Auch die im Rahmen dieser Dissertation gesammelten Daten sprechen tendenziell für die Sinnhaftigkeit dieses Vorgehens: Mithilfe orientierender Verfahren konnte die überwiegende Mehrzahl kognitiv beeinträchtigter Patienten identifiziert werden. Ein Abgleich mit den Ergebnissen der Tests in der ausführlichen Testbatterie zeigt aber, dass die hier objektivierten Defizite nicht unbedingt in dieselben Domänen fallen, wie durch das Screening nahegelegt wird. Somit zeigt sich auch hier, dass sehr große interindividuelle Unterschiede in Form und Ausprägung der kognitiven

Beeinträchtigungen bestehen können. Bereits frühere Studien (Ryan et al., 1996; Fischer et al., 1998) legten nahe, dass die größte Gruppe der MS-Patienten eher leicht- bis mäßiggradige kognitive Beeinträchtigungen aufweist. Die größte Schwierigkeit im diagnostischen Prozess besteht also zunächst in der Differenzierung zwischen diesen Patienten und den kognitiv unbeeinträchtigten Patienten, da die Identifizierung schwer beeinträchtigter Patienten vergleichsweise leicht fallen dürfte. Das kognitive Screening scheint geeignet zu sein, diese Einteilung zu ermöglichen, wohingegen die ausführliche Testung eine differenziertere Einschätzung spezifischer Teilleistungen erlaubt. Das zugrundeliegende Rational könnte also als ‚Alles-oder-nichts-Prinzip' beschrieben werden: Wenn im Screening alles unauffällig ist, d.h. wenn sich in erster Linie im Bereich der Informationsverarbeitungsgeschwindigkeit keine Hinweise auf Beeinträchtigungen zeigen, wird nicht davon ausgegangen, dass kognitive Defizite bestehen, und lediglich eine Verlaufskontrolle terminiert. Wenn das Screening jedoch ein auffälliges Ergebnis zeigt, könnten sich in der ausführlichen Testung theoretisch in allen Domänen Beeinträchtigungen finden. Diese Beschreibung ist etwas vereinfacht, da in dem in dieser Dissertation zur Anwendung gekommenen Screening-Verfahren auch andere kognitive Domänen erfasst wurden, aber grundsätzlich beschreibt sie das Testrational korrekt.

Das Vorgehen ist somit sowohl für den Patienten als auch für den Diagnostiker ressourcenschonend, das Argument der Ökonomie wäre damit erfüllt. Seine Daseinsberechtigung bezieht es aber aus der Tatsache, dass es sich im klinischen Alltag in der überwiegenden Zahl der Fälle bewährt hat, wie auch die Ergebnisse der empirischen Studien nahelegen.

Diese Erwägungen lassen Raum für kritische Fragen, und einige dieser Aspekte sollen hier angesprochen werden:

1. *Was ist mit den immerhin 20% fälschlicherweise vom Screening als unauffällig identifizierten Patienten? Sollte ein Screening nicht höhere Sensitivitätswerte aufweisen?*

   Hier sei zunächst darauf verwiesen, dass wir letztlich auch durch die ausführliche Testung keinen ‚wahren Wert' der kognitiv beeinträchtigten Patienten ermitteln können, sondern sowohl Screening als auch ausführliche Testung diesen Wert jeweils nur schätzen. Da wir aber davon ausgehen, dass die ausführliche Testung einen besseren, umfassenderen Prädiktor auf einer breiteren Datenbasis darstellt, wird dieser als Goldstandard deklariert. Trotzdem sollte nicht ausgeschlossen werden, dass einige der im Screening zur Anwendung kommenden Verfahren im Zusammenhang mit MS eine besonders hohe ökologische Validität haben und in dieser Hinsicht der ausführlichen Diagnostik vielleicht sogar überlegen sind. Als konkretes Beispiel sei hier auf den SDMT verwiesen. Dies wird unter anderem auch durch die Ergebnisse unserer Übersichtsarbeit nahegelegt. Trotzdem muss eingeräumt werden, dass höhere Werte für Sensitivität und Spezifität wünschenswert gewesen wären. Möglicherweise ist auch die Komposition des Screenings noch nicht optimal, oder die Cut-Off-Werte wurden unvorteilhaft gewählt.

2. *Wie ist die Alltagsrelevanz dieser Ergebnisse einzuordnen? Besitzen die Testverfahren einen Bezug zur Lebensrealität der Patienten?*

   Dies ist sicherlich die von Patienten selbst am häufigsten vorgetragene Kritik an den durchgeführten neuropsychologischen Verfahren. Allerdings handelt es sich dabei kaum um ein MS-spezifisches Problem. Der grundlegende Einwand, dass eine Laborsituation niemals in

Gänze die Realität widerspiegeln kann, lässt sich nicht vollständig entkräften. Zur Beurteilung der Alltagsrelevanz empfiehlt sich umso mehr die Durchführung einer ausführlichen Testbatterie, da hier auch Aspekte wie Daueraufmerksamkeit, Erschöpfung oder Ablenkbarkeit in den Fokus rücken, und neben domänenspezifischen Tests auch Platz für die Durchführung alltagsnäherer Verfahren ist.

3. *Wie hoch ist der Einfluss konfundierender Faktoren wie Depressivität oder kognitiver Fatigue? Gibt es einen Einfluss der Tagesform?*

   Dies sind wichtige Punkte, welche sich ebenfalls potentiell reduzierend auf die Sensitivität und Spezifität des Screenings auswirken können. Tatsächlich berichten viele MS-Patienten über markante Leistungsschwankungen im Tagesverlauf, aber auch tagesformabhängige Schwankungen. Der Diagnostiker sollte sich – wie bei anderen Störungsbildern auch – nie blind auf die Ergebnisse der Testverfahren verlassen, sondern muss letztlich Testergebnisse, Anamnese, subjektive Beschwerdeschilderungen und ggf. Fremdanamnese zu einem konsistenten Gesamtbild integrieren.

4. *Wäre es nicht sinnvoller, Screening und ausführliche Testung zusammenzulegen, damit jedem Patienten eine ausführliche Diagnostik zuteilwird?*

   Das zweistufige Diagnostikverfahren sollte angewendet werden, weil es sich als ökonomisch erwiesen hat und auch dem Patienten unnötige Untersuchungen erspart. In diesem Zusammenhang sollte auch auf die häufig geforderte Vermeidung von ‚Overtesting' hingewiesen werden, was hiermit erfüllt wäre. Ein etabliertes Screeningverfahren wie die Kurzform der BRB sollte angewendet werden, weil es sich als hinreichend valides Prognoseinstrument bewährt hat. Die ausführliche Testung sollte sich in etwa an der in Abbildung 1 dargestellten Testbatterie orientieren, da die enthaltenen Verfahren einen guten Überblick über die einzelnen Teilleistungen erlauben und sich für sich genommen im Zusammenhang mit MS ebenfalls bereits bewährt haben. Davon unbesehen bleibt eine Erweiterung der Testbatterie zur Klärung spezifischer Fragestellungen möglich.

5. *Wieso besteht die Notwendigkeit regelmäßiger Verlaufskontrollen?*

   Da es sich bei MS um eine fortschreitende Erkrankung handelt, ist das Ergebnis einer neuropsychologischen Diagnostik letztlich nur eine Momentaufnahme. Um eine mögliche Progredienz möglichst früh zu erkennen, sind regelmäßige - idealerweise jährliche - Verlaufskontrollen zumindest bei volatilen Verlaufsformen dringend indiziert. Diese erfüllen denselben Zweck wie regelmäßige bildgebende Diagnostik, indem sie eine Veränderung des Ausgangszustands erkennbar machen sollen. Hier zeigt sich erneut ein maßgeblicher Vorteil des zweigeteilten diagnostischen Vorgehens, denn kognitiv unbeeinträchtigte Patienten sollten - ebenfalls im jährlichen Verlauf - lediglich mit dem Screening-Verfahren untersucht werden. Bei über lange Zeit unbeeinträchtigten Patienten summier sich der ökonomische Nutzen einer Kurztestung also im Lauf der Jahre.

Zusammenfassend kann festgehalten werden, dass es viele gute Gründe für das zweistufige Vorgehen bei der neuropsychologischen Diagnostik von MS-Patienten gibt. Diesen liegen neuroanatomische, testtheoretische, ökonomische und letztlich auch anwenderbezogene Überlegungen zugrunde. Im Gegensatz dazu sprechen keine zwingenden Argumente gegen das beschrieben Vorgehen, so dass der aktuelle Diagnoseansatz als beibehaltenswert angesehen werden sollte.

5.5 Limitationen

Hinsichtlich der Interpretation der in den empirischen Studien erbrachten Ergebnisse muss auf einige Einschränkungen hingewiesen werden:

In der ersten empirischen Studie vergingen zwischen initialem neuropsychologischen Screening und ausführlicher Testung teilweise mehrere Monate. Dieses Intervall ist darauf zurückzuführen, dass die Stichprobe im Rahmen der klinischen Routine erhoben wurde, und dieser Zeitraum dem Abstand zwischen zwei ambulanten Untersuchungszeitpunkten entsprach. Folglich ließ sich aufgrund der Art der Erhebung dieses Intervall nicht vermeiden. Trotzdem muss darauf hingewiesen werden, dass eine zeitnahe, möglichst unmittelbare Folge von Screening und ausführlicher Testung im Rahmen einer Validierungsstudie zu bevorzugen gewesen wäre. Dies gilt insbesondere vor dem Hintergrund, dass es sich bei MS um eine Krankheit handelt, bei der es schubbedingt auch innerhalb kurzer Zeiträume zu großen intraindividuellen Leistungsschwankungen kommen kann.

In Bezug auf die Ergebnisse der zweiten empirischen Studie ist noch einmal deutlich darauf hinzuweisen, dass keine Überprüfung von Sensitivität und Spezifität der Kurzform der BRB mit dem FPT vorgenommen wurde. Vielmehr wurden beide Screening-Kombinationen miteinander verglichen, ohne die Ergebnisse eines Goldstandards zugrunde zu legen. Eine Überprüfung der alternativen Kurzform der BRB hinsichtlich Sensitivität und Spezifität steht insofern noch aus. Bei allem gebotenen Optimismus in Bezug auf den FPT ist insbesondere im Zusammenhang mit MS ebenfalls noch zu klären, ab welchem Punkt motorische Defizite zu einer derart signifikanten Beeinträchtigung bei der Bearbeitung führen, dass sie die Ergebnisinterpretation fragwürdig erscheinen lassen. Ein Abgleich mit feinmotorischen Fähigkeiten – zum Beispiel anhand einer Steckbrettaufgabe – wäre ein erster Schritt, um dieser Frage nachzugehen.

Wünschenswert wäre darüber hinaus ein Abgleich des prädiktiven Wertes der beiden etablierten Screening-Verfahren BRB und BICAMS anhand eines einheitlichen Goldstandards. Dies würde erstmals eine statistisch fundierte Beurteilung der Frage ermöglichen, ob einer der beiden Ansätze dem Anderen überlegen sein könnte.

In Bezug auf die Übersichtsarbeit ist darauf hinzuweisen, dass diese zwar als wichtige Grundlage zur Identifizierung der bei MS sinnvollerweise einsetzbaren neuropsychologischen Tests dienen kann, allerdings keine Zusammenfassung der konsultierten Studien zu Metadaten beinhaltet. Eine aktuelle Metaanalyse, welche die statistische und quantitative Aufarbeitung der Studiendaten der letzten Jahre beinhaltet, steht somit weiterhin aus.

5.6 Zusammenfassung und Ausblick

Die Ergebnisse der vorliegenden Dissertation bestätigen den grundsätzlichen Nutzen eines zweigeteilten diagnostischen Vorgehens bei MS mit initialem neuropsychologischen Screening und bei Bedarf anschließender ausführlicher neuropsychologischer Testung. Weiterhin werden empirische Belege für die Validität der Kurzform der BRB und den Nutzen eines adaptierten Screeningverfahrens mit dem FPT präsentiert. Anhand der Übersichtsarbeit lassen sich auch Hinweise über die Validität einzelner Testverfahren der ausführlichen Testbatterie und über deren prognostischen Nutzen ableiten. Insbesondere in Bezug auf den FPT sind weitere Studien erforderlich, um eine Aussage über den prognostischen Wert und die Validität im Zusammenhang mit feinmotorisch beeinträchtigten Patienten treffen zu können.

Für die weitere Forschung auf dem Gebiet der Neuropsychologie der MS bleiben aber noch viele Fragen unbeantwortet. Eine wichtige Frage in diesem Zusammenhang ist die nach dem richtigen Intervall der Verlaufskontrollen. Ist es sinnvoll, einen Patienten immer wieder in jährlichen Intervallen mit denselben Testverfahren zu untersuchen? Ist es stattdessen möglich, Marker wie Verlaufsform oder Schubhäufigkeit zu identifizieren, welche das optimale Intervall von Verlaufskontrollen indizieren? Oder kann im Gegenteil eine neuropsychologische Untersuchung ähnlich einem MRT tatsächlich als reliabler Indikator für Schubaktivität dienen? Weiterhin dringlich wäre im Zusammenhang mit Verlaufskontrollen die Klärung der Frage, ob die Validität der eingesetzten Testverfahren bei mehrfacher Anwendung nicht empfindlich leidet.

Im Zusammenhang mit der Objektivität der eingesetzten Verfahren stellt sich die Frage, ob es sinnvoll sein könnte, die Durchführung der Screenings in die Hände nicht-psychologischer Mitarbeiter (z.B. Studienassistenten oder MS-Nurses) zu geben? Dies würde in großen MS-Zentren Kapazitäten im Bereich ausführlicher Diagnostik und Therapie eröffnen, und darüber hinaus in kleineren neurologischen Praxen ohne ansässigen Neuropsychologen eine neuropsychologische Minimaldiagnostik ermöglichen. Andererseits stellt die psychologische Expertise in den Bereichen Verhaltensbeobachtung, Anamnese und Exploration vermutlich einen wichtigen Faktor dar, um ambivalente oder grenzwertige Screening-Ergebnisse in den richtigen Kontext einzuordnen.

Zuletzt sollte auch der Frage nach dem weiteren Nutzen der neuropsychologischen Diagnostik vermehrt nachgegangen werden: Aus der Identifikation neuropsychologischer Beeinträchtigungen lässt sich nicht nur Krankheitsaktivität ablesen, sondern auch ein neuropsychologischer Behandlungsauftrag ableiten. Allerdings sind die Evidenzen für z.B. PC-gestütztes neuropsychologisches Training bei MS bisher ausgesprochen ernüchternd. Neue Therapieansätze wie zum Beispiel Neurofeedbacktraining oder Achtsamkeitsübungen müssen sich der Herausforderung einer kritischen wissenschaftlichen Überprüfung unterziehen.

6. Literatur

Amato, M. P., Zipoli, V. & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *Journal of the neurological sciences*, *245* (1), 41–46.

Amato, M. P., Zipoli, V. & Portaccio, E. (2008). Cognitive changes in multiple sclerosis. *Expert review of neurotherapeutics*, *8* (10), 1585–1596.

Archibald, C. J. & Fisk, J. D. (2000). Information processing efficiency in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *22* (5), 686–701.

Aschenbrenner, S., Tucha, O. & Lange, K. W. (2000). *Regensburger Wortflüssigkeits-Test: RWT*. Hogrefe, Verlag für Psychologie.

Beblo, T. & Lautenbacher, S. (2006). *Neuropsychologie der Depression. Band 6 in Fortschritte der Neuropsychologie*. Göttingen: Hogrefe Verlag.

Benedict, R. H. B. (1997). *Brief visuospatial memory test-revised: professional manual. Odessa, Florida: Psychological Assessment Resources*. Inc.

Benedict, R. H. B., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., … Munschauer, F. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. *The Clinical Neuropsychologist*, *16*(3), 381-397.

Benedict, R. H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N. et al. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12* (04), 549–558.

Benton, A. L. (1994). *Contributions to neuropsychological assessment: A clinical manual*. Oxford University Press, USA.

Bergendal, G., Fredrikson, S. & Almkvist, O. (2007). Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *European neurology*, *57* (4), 193–202.

Buschke, H. & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*, *24* (11), 1019–1019.

Calabrese, P. (2006). Neuropsychology of multiple sclerosis. *Journal of Neurology*, *253*, i10–i15.

Calabrese, M., Agosta, F., Rinaldi, F., Mattisi, I., Grossi, P., Favaretto, A. et al. (2009). Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Archives of neurology*, *66* (9), 1144–1150.

Carton, H., Vlietinck, R., Debruyne, J., De Keyser, J., D'Hooghe, M.-B., Loos, R. et al. (1997). Risks of multiple sclerosis in relatives of patients in Flanders, Belgium. *Journal of Neurology, Neurosurgery & Psychiatry*, *62* (4), 329–333.

Chelune, G. J., Stott, H., & Pinkston, J. (2008). *Multiple Sclerosis Textbook of Clinical Neuropsychology*. New York, NY: Taylor and Francis.

Chiaravalloti, N. D. & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7* (12), 1139–1151.

Chiaravalloti, N. D., Balzano, J., Moore, N. B. & DeLuca, J. (2009). The Open-Trial Selective Reminding Test (OT-SRT) as a tool for the assessment of learning and memory. *The Clinical Neuropsychologist*, *23* (2), 231–254.

Comi, G., Rovaris, M., Leocani, L., Martinelli, V. & Filippi, M. (2000). Assessment of the damage of the cerebral hemispheres in MS using neuroimaging techniques. *Journal of the neurological sciences*, *172*, S63–S66.

Compston, A., Coles, A. (2008). *Multiple Sclerosis*. Lancet, *372*, 1502-1517.

DeLuca, J., Gaudino, E. A., Diamond, B. J., Christodoulou, C. & Engel, R. A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *20* (3), 376–390.

DeLuca, J., Chelune, G. J., Tulsky, D. S., Lengenfelder, J. & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of clinical and experimental neuropsychology*, *26* (4), 550–562.

Denney, D. R., Sworowski, L. A. & Lynch, S. G. (2005). Cognitive impairment in three subtypes of multiple sclerosis. *Archives of Clinical Neuropsychology*, *20* (8), 967–981.

DeSousa, E. A., Albert, R. H. & Kalman, B. (2002). Cognitive impairments in multiple sclerosis: a review. *American journal of Alzheimer's disease and other dementias*, *17* (1), 23–29.

Diener, H.-C., Weimar, C., Berlit, P., Dueschl, G., Elger, C., Gold, R. et al. (2012). *Leitlinien für Diagnostik und Therapie in der Neurologie. 5*. Thieme.

Drew, M., Tippett, L. J., Starkey, N. J. & Isler, R. B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. *Archives of Clinical Neuropsychology*, *23* (1), 1–19.

Dusankova, J. B., Kalincik, T., Havrdova, E. & Benedict, R. H. (2012). Cross cultural validation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) and the brief international cognitive assessment for multiple sclerosis (BICAMS). *The Clinical Neuropsychologist*, *26* (7), 1186–1200.

Dyment, D. A., Yee, I. M. L., Ebers, G. C. & Sadovnick, A. D. (2006). Multiple sclerosis in stepsiblings: recurrence risk and ascertainment. *Journal of Neurology, Neurosurgery & Psychiatry*, *77* (2), 258–259.

Ebers, G. C., Sadovnick, A. D. & Risch, N. J. (1995). A genetic basis for familial aggregation in multiple sclerosis. *Nature*, *377* (6545), 150.

Fischer, J. S., Foley, F. W., Aikens, J. E., Ericson, G. D., Rao, S. M. & Shindell, S. (1994). What do we really know about cognitive dysfunction, affective disorders, and stress in multiple sclerosis? A practitioner's guide. *Journal of Neurologic Rehabilitation*, *8* (3), 151–164.

Fischer, J. S., Jacobs, L. D., Cookfair, D. L. & Rudick, R. A. (1998). Heterogeneity of cognitive dysfunction in multiple sclerosis. *The Clinical Neuropsychologist,12*, 286.

Fischer, J. S., Rudick, R. A., Cutter, G. R. & Reingold, S. C. (1999). The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment. *Multiple Sclerosis Journal*, *5* (4), 244–250.

Fisk, J. D. & Archibald, C. J. (2001). Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis. *Journal of the International Neuropsychological Society*, *7* (03), 363–372.

Forn, C., Belenguer, A., Parcet-Ibars, M. A. & Avila, C. (2008). Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). *Journal of clinical and experimental neuropsychology*, *30* (7), 789–796.

Franklin, G. M., Heaton, R. K., Nelson, L. M., Filley, C. M. & Seibert, C. (1988). Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis. *Neurology*, *38* (12), 1826–1826.

Gauggel, S. & Sturm, W. (2005). Leitlinien der Gesellschaft für Neuropsychologie (GNP) für neuropsychologische Diagnostik und Therapie. *Zeitschrift für Neuropsychologie*, *16* (4), 175–199.

Goebel, S., Atanassov, L., Köhnken, G., Mehdorn, H. M. & Leplow, B. (2013). Understanding quantitative and qualitative figural fluency in patients with Parkinson's disease. *Neurological Sciences*, *34* (8), 1383–1390.

Goebel, S., Fischer, R., Ferstl, R. & Mehdorn, H. M. (2009). Normative data and psychometric properties for qualitative and quantitative scoring criteria of the Five-point Test. *The Clinical Neuropsychologist*, *23* (4), 675–690.

Gold, R.M., Wiendl, H. & Hemmer, B. (2014). DGN-Leitlinie Diagnostik und Therapie der Multiplen Sklerose. *Aktuelle Neurologie, 41* (06), 326-327.

Goodkin, D. E., Hertsgaard, D. & Seminary, J. (1988). Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg tests. *Archives of physical medicine and rehabilitation*, *69* (10), 850–854.

Hammond, S. R., English, D. R. & McLeod, J. G. (2000). The age-range of risk of developing multiple

sclerosis. *Brain*, *123* (5), 968–974.
Härting, C., Markowitsch, H. J., Neufeld, H., Calabrese, P., Deisinger, K. & Kessler, J. (2000). Die Wechsler-Memory-Scale-revised. *Deutschsprachige Adaptation. Bern: Huber*.
Heaton, R. K., Chelune, G. J., Curtiss, G., Kay, G. G. & Talley, J. L. (1993). *Wisconsin card sorting test*. Psychological Assessment Resources.
Hoffmann, S., Tittgemeyer, M. & von Cramon, D. Y. (2007). Cognitive impairment in multiple sclerosis. *Current opinion in neurology*, *20* (3), 275–280.
Jasse, L., Vukusic, S., Durand-Dubief, F., Vartin, C., Piras, C., Bernard, M. et al. (2013). Persistent visual impairment in multiple sclerosis: prevalence, mechanisms and resulting disability. *Multiple Sclerosis Journal*, *19*(12), 1618–1626.
Kujala, P., Portin, R. & Ruutiainen, J. (1997). The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. *Brain*, *120* (2), 289–297.
Kurtzke, J. F. (1975). A reassessment of the distribution of multiple sclerosis. *Acta Neurologica Scandinavica*, *51* (2), 110–136.
Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). *Neurology*, *33* (11), 1444–1444.
Kurtzke, J. F. (1993). Epidemiologic evidence for multiple sclerosis as an infection. *Clinical microbiology reviews*, *6* (4), 382–427.
Lang, H. L., Jacobsen, H., Ikemizu, S., Andersson, C., Harlos, K., Madsen, L. et al. (2002). A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nature immunology*, *3* (10), 940–943.
Langdon, D. W., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S. et al. (2012). Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Multiple Sclerosis Journal*, *18* (6), 891–898.
Levin, L. I., Munger, K. L., Rubertone, M. V., Peck, C. A., Lennette, E. T., Spiegelman, D. et al. (2003). Multiple sclerosis and Epstein-Barr virus. *Jama*, *289* (12), 1533–1536.
Lezak, M. D. (2012). *Neuropsychological assessment*. Oxford University Press, USA.
Lynch, S. G., Dickerson, K. J. & Denney, D. R. (2010). Evaluating processing speed in multiple sclerosis: a comparison of two rapid serial processing measures. *The Clinical Neuropsychologist*, *24* (6), 963–976.
Martyn, C. N., Cruddas, M. & Compston, D. A. (1993). Symptomatic Epstein-Barr virus infection and multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *56* (2), 167–168.
McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H.-P., Lublin, F. D. et al. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of neurology*, *50* (1), 121–127.
Moreno, M. J. G., García, M. C., Marasescu, R., González, A. P., & Benito, Y. A. (2013). Neuropsychological syndromes in multiple sclerosis. *Psicothema*, *25*(4), 452–460.
Niemann, H., Sturm, W., Thöne-Otto, A. I. & Willmes, K. (2008). CVLT California verbal learning test. German adaptation. Manual.
Parmenter, B. A., Zivadinov, R., Kerenyi, L., Gavett, R., Weinstock-Guttman, B., Dwyer, M. G. et al. (2007). Validity of the Wisconsin card sorting and Delis–Kaplan executive function system (DKEFS) sorting tests in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *29* (2), 215–223.
Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C. & Hames, K. (1998). Impairments of attention in individuals with multiple sclerosis. *Multiple Sclerosis Journal*, *4* (5), 433–439.
Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H.-P., Kappos, L. et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Annals of neurology*, *58* (6), 840–846.
Portaccio, E., Goretti, B., Zipoli, V., Siracusa, G., Sorbi, S. & Amato, M. P. (2009). A short version of Rao’s Brief Repeatable Battery as a screening tool for cognitive impairment in multiple sclerosis. *The Clinical Neuropsychologist*, *23* (2), 268–275.
Potagas, C., Giogkaraki, E., Koutsis, G., Mandellos, D., Tsirempolou, E., Sfagos, C. et al. (2008).

Cognitive impairment in different MS subtypes and clinically isolated syndromes. *Journal of the neurological sciences*, *267* (1), 100–106.

Rao, S. M., Hammeke, T. A., McQuillen, M. P., Khatri, B. O. & Lloyd, D. (1984). Memory disturbance in chronic progressive multiple sclerosis. *Archives of neurology*, *41* (6), 625–631.

Rao, S. M. (1990). A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. *Milwaukee: Medical College of Wisconsin*.

Rao, S. M., Leo, G. J., Bernardin, L. & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, *41* (5), 685–691.

Rao, S. M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G. J. et al. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology*, *7* (3), 364.

Regard, M., Strauss, E. & Knapp, P. (1982). Children's production on verbal and non-verbal fluency tasks. *Perceptual and motor skills*, *55* (3), 839–844.

Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique.(Les problems.). *Archives de psychologie*.

Robertson, N. P., Clayton, D., Fraser, M., Deans, J. & Compston, D. A. S. (1996). Clinical concordance in sibling pairs with multiple sclerosis. *Neurology*, *47* (2), 347–352.

Rogers, J. M. & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. *Journal of Clinical Neuroscience*, *14* (10), 919–927.

Ryan, L., Clark, C. M., Klonoff, H., Li, D. & Paty, D. (1996). Patterns of cognitive impairment in relapsing–remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. *Neuropsychology*, *10* (2), 176.

Sandry, J., Paxton, J. & Sumowski, J. F. (2016). General mathematical ability predicts PASAT performance in ms patients: Implications for clinical interpretation and cognitive reserve. *Journal of the International Neuropsychological Society*, *22* (03), 375–378.

Savettieri, G., Messina, D., Andreoli, V., Bonavita, S., Caltagirone, C., Cittadella, R. et al. (2004). Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis. *Journal of neurology*, *251* (10), 1208–1214.

Shah, A. (2009). Fatigue in multiple sclerosis. *Physical medicine and rehabilitation clinics of North America*, *20* (2), 363–372.

Smith, A. (1982). Symbol digit modalities test (SDMT) manual (revised) Western Psychological Services. *Los Angeles*.

Sonder, J. M., Burggraaff, J., Knol, D. L., Polman, C. H. & Uitdehaag, B. M. (2014). Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Multiple Sclerosis Journal*, *20* (4), 481–488.

Stegen, S., Stepanov, I., Cookfair, D., Schwartz, E., Hojnacki, D., Weinstock-Guttman, B. et al. (2010). Validity of the California Verbal Learning Test–II in multiple sclerosis. *The Clinical Neuropsychologist*, *24* (2), 189–202.

Stenager, E., Knudsen, L. & Jensen, K. (1989). Multiple sclerosis: correlation of cognitive dysfunction with Kurtzke disability status scale. *Mental disorders and cognitive deficits in multiple sclerosis. London: Libbey*, 27–37.

Strauss, E., Sherman, E. M. & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. American Chemical Society.

Tucha, O. & Lange, K. W. (2004). *Turm von London: Deutsche Version, TL-D*. Hogrefe.

Warrington, E. K. & James, M. (1991). *The visual object and space perception battery*. Thames Valley Test Company Bury St Edmunds.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*.

Willer, C. J., Dyment, D. A., Risch, N. J., Sadovnick, A. D., Ebers, G. C. & Group, C. C. S. (2003). Twin concordance and sibling recurrence rates in multiple sclerosis. *Proceedings of the National Academy of Sciences*, *100* (22), 12877–12882.

Zakzanis, K. K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. *Archives of Clinical Neuropsychology*, *15* (2), 115–136.

Zimmermann, P. & Fimm, B. (2009). *Testbatterie zur Aufmerksamkeitsprüfung-Version 2.2:(TAP);[Handbuch]*. Psytest.

7. Anhang

Publikation 1: *Hansen, S. & Lautenbacher, S. (2017) Neuropsychological assessment in multiple sclerosis: an overview*. *Zeitschrift für Neuropsychologie, 28 (2), 117-148..*

Publikation 2: *Hansen, S., Münßinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P. & Keune P.M. (2015) Cognitive screeningtools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. BMC Neurology, 15 (1),246-253.*

Publikation 3: *Hansen, S., Münßinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P. & Keune, P.M. (2017) Cognitive screening in multiple sclerosis: the Five-Point-Test as a substitute for the PASAT in measuring executive function. The Clinical Neuropsychologist, 31 (1), 179-192.*

Hansen et al. BMC Neurology (2015) 15:246
DOI 10.1186/s12883-015-0497-8

BMC Neurology

RESEARCH ARTICLE Open Access

Cognitive screening tools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery

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Abstract

Background: Cognitive deficits are common in multiple sclerosis (MS) and require continuous monitoring. In routine examinations, screening instruments such as the Brief Repeatable Battery (BRB) may serve this purpose. It was suggested that even a shortened version of the BRB, comprising the Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT) and Selective Reminding Test (SRT), may be feasible. However, an evaluation of sensitivity and specificity of the short BRB in comparison to an independent battery of established tests has not yet occurred. Therefore in the current study, this short version of the BRB was matched against the gold standard of an extensive test battery comprehensively assessing neuropsychological functions.

Methods: 127 MS-patients were tested with a short version of the BRB and an extensive procedure. The latter served as the gold standard for defining sensitivity and specificity.

Results: For subtests of the short BRB, estimates of sensitivity (38-44 %) and specificity (81-94 %) were obtained. Combining subtests into a single indicator of cognitive deficits yielded increased sensitivity (78 %), while reducing specificity (65 %).

Conclusion: The short BRB is reasonably sensitive and specific in detecting cognitive deficits. However, these qualities only emerge, if the short BRB is administered as a whole, whereas sensitivity is considerably lower than suggested by previous work, when relying on subtests separately (SDMT, PASAT, SRT). While the short BRB may not be regarded as conclusive as an extensive test battery, it represents a valid and economic screening instrument.

Keywords: Cognitive impairment, Multiple sclerosis (MS), Screening, Brief repeatable battery (BRB)

Background

Neuropsychological deficits occur in about 40-65 % of patients diagnosed with multiple sclerosis (MS). Deficits in attention and information-processing speed as well as long-term and working memory are most common, [1] whereas language and general intellectual ability seem to be largely unaffected [2].

Although these deficits exert a profound impact on patients' quality of life, they frequently remain undiscovered during routine clinical examinations [3, 4]. This may be attributed to the fact that in clinical practice, time for exhaustive neuropsychological assessments is sparse. In the past, this problem has been acknowledged and tackled by employing short test batteries with the explicit purpose of diagnosing cognitive deficits in MS [5, 6]. Among them, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) [6] and the Brief Repeatable Battery of Neuropsychological Tests (BRB) [7, 8] have been widely accepted as valid screening tools for testing MS-patients [6, 9–11]. The BICAMS is

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extremely short, taking up only approximately 15 minutes of testing time, while the BRB entails a relatively lengthy testing procedure of approximately 90 minutes duration. However in the BICAMS, there is a decisive lack of assessment of executive functions, since it focuses on processing speed as well as verbal and nonverbal memory [6].

In a pioneering study by Portaccio et al., the performance of a shortened version of the BRB as a quick and economic screening tool was assessed [12]. This short form of the BRB comprises the Paced Auditory Serial Addition Test (PASAT), addressing working memory and attention, the Symbol Digit Modalities Test (SDMT), referring to attention and information processing speed, as well as the Selective Reminding Test (SRT) assessing verbal memory. The authors report that failure on one of these three subtests predicted neuropsychological deficits with high sensitivity (94 %) and specificity (84 %).

While the latter findings are promising concerning the application as a brief assessment tool, they need to be interpreted in the context of a noteworthy limitation. In particular, the authors examined sensitivity and specificity of the aforementioned subtests with regards to cognitive deficits, as determined by the whole BRB and an additional Stroop Test for additional information regarding potential executive dysfunction. Consequently, there was a considerable overlap of tests included in the short screening version of the BRB on the one hand (PASAT, SDMT, SRT), and the procedure which was implemented to derive reliable information about the actual presence of cognitive deficits on the other hand (BRB and Stroop Test). One may argue that similar classification patterns between the shortened version of the BRB and the extended procedure (BRB and Stroop Test) may have been confounded by the fact that all tests of the short version of the BRB were actually included in the more extensive procedure. By this reasoning, estimates of sensitivity and specificity might have been distorted.

The purpose of the current study was to reassess the findings of the pioneering study by Portaccio et al. [12] while avoiding its methodological bias. Thus, a more economic neuropsychological testing of MS patients during clinical routine could be achieved. To this end, sensitivity and specificity of the short version of the BRB were examined with regards to the presence or absence of cognitive deficits as determined by an extensive neuropsychological diagnostic procedure not including the BRB subtests in question. The latter procedure of two hours duration was implemented to thoroughly examine all cognitive domains which may be found deficient in MS-patients. The use of further tests in the screening-procedure (including the Stroop Test) for validation – although desirable – would have significantly hampered the aim of keeping the screening short and was therefore relinquished.

Methods

Subjects

A group of 127 patients diagnosed with MS was recruited in the Department of Neurology, Klinikum Bayreuth GmbH, Germany, during the routine clinical process. Data collection was planned before the screening and extensive testing procedure were executed. Recruitment took place from August 2012 to February 2014.Inclusion criteria involved an MS diagnosis according to McDonald criteria [13] and an age range between 18-75 years. Patients were not eligible for study entry if they had severe motor or visual impairments that interfered with handling test material. Demographics and information about clinical characteristics were extracted from patients' files held by the Department of Neurology, as displayed in Table 1. Participation was voluntary, and all participants provided written informed consent prior to study entry. The study was approved by the ethics committee of the University of Bayreuth.

Table 1 Demographical and clinical characteristics of the sample

	CIS	RR-MS	SP-MS	PP-MS	Whole sample
N (%)	11 (8.7)	85 (66.9)	29 (22.8)	2 (1.6)	127 (100)
Age					
Mean	41.6	40.7	50.3	55.0	42.9
SD	9.6	10.3	8.9	28.3	11.0
Min	26	18	28	35	18
Max	54	62	69	75	75
Female sex (%)	8 (72.7)	53 (62.4)	23 (79.3)	1 (50.0)	85 (66.9)
Education					
0-9 years (%)	3 (27.3)	32 (37.6)	13 (44.8)	0 (0.0)	48 (37.8)
10-12 years (%)	4 (36.4)	22 (25.9)	11 (37.9)	2 (100)	39 (30.7)
13+ years (%)	4 (36.4)	31 (36.5)	5 (17.2)	0 (0.0)	40 (31.5)
EDSS					
Median	1	2	4	4	2.5
SD	1.5	1.2	1.3	0	1.8
Min	0	0	4	4	0
Max	4	6	8.5	4	8.5
Disease duration					
Mean	4.01	7.77	16.97	9.6	9.56
SD	4.64	6.91	12.03	7.64	9.2
Min	0	0	1.7	4.2	0
Max	13	35.7	49.7	15	49.7

EDSS = Expanded Disability Status Scale, SD = Standard Deviation

Procedure

All tests were administered in a standardized individual setting during the routine clinical process. Patients were initially tested with the screening tool, i.e. the short version of the BRB, [12] which took approximately 30 minutes. Testing was conducted by highly trained psychologists specialized in neuropsychology, who could access patients files and clinical information. The procedure comprised the short screening subtests devised by Portaccio et al. [12], namely the Selective Reminding Test (SRT), Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT).

Subsequently, a comprehensive diagnostic procedure was executed, which was implemented to derive reliable information about the actual presence of cognitive deficits. This was scheduled to take place at the patient's subsequent routine clinical examination (Mean = 4.2 months, SD = 4.2 months). In this context, an extensive neuropsychological test battery was administered. The comprehensive diagnostic procedure had a duration of approximately two hours.

Measures

Screening tool

Following suggestions of Portaccio et al. [12], the short form of the BRB included the SRT for the assessment of declarative episodic long-term memory. Initially, a 12-word list was read to the patient who was required to recall as many words as possible. Afterwards, the clinician reread the words missed by the patient, who had to try and recall the complete list again. This procedure was repeated for a maximum of six trials. The test yields two parameters, i.e. long-term storage (LTS) and consistent long-term retrieval (CLTR). For further information on these parameters, see Additional file 1: Supplement 1.

As a further component, the SDMT [14], assessing information processing speed and attention was included. Patients were required to verbally pair numbers and symbols according to a fixed pattern, the outcome score being the amount of pairings solved correctly within 90 seconds.

Finally the PASAT [15] as a measure of working memory and attention in its three-second interstimulus-interval (ISI) version was applied. Single-digit numbers are read to the patient from tape. The patient has to add each number to the one immediately prior to it. A maximum of 60 correct responses can be achieved. Outcome parameters are listed in Additional file 1: Supplement 2.

Extensive neuropsychological test procedure

In addition to the screening tool, an extensive battery of neuropsychological tests was implemented, in order to reliably determine the presence of putative cognitive deficits. The extensive test battery was composed closely adhering to standards set by Benedict [5] as well as Langdon et al. [6]

Long-term and working memory

The California Verbal Learning Test (CVLT) [16] was included to assess declarative episodic verbal memory functioning. The paradigm includes five learning-trials of a 16-item word list. Words fall into one of four semantic categories. After the fifth trial, patients were confronted with a distractor-list and a subsequent task to recall items of the initial list. A delayed recall task was implemented after approximately 20 minutes.

To address working memory capacity, two subtests of the Wechsler Memory Scale (WMS-R) [17] were implemented. The first test (digit span forward) required a patient to instantly repeat strings of numbers of increasing length, read out by the examiner. In a variation of this task (digit span backwards) numbers were to be reproduced in reversed order. The second subtest (block span), was a nonverbal equivalent of the digit span task. Patients were required to reproduce several sequences of increasing length on a tapping board (forwards and backwards). It should be noted that particularly the backwards conditions of these tasks address working memory capacity, whereas performance in the forward conditions is also affected by general cognitive processing speed.

Attention

Attentional parameters were assessed by means of a standardized, computer-based Test of Attentional Performance (TAP) [18]. Three subtests were used:

Alertness

Motor response times were obtained in two conditions. First, patients were required to respond to a cross appearing in the middle of the screen (variable ISI) by pressing a button as quickly as possible, yielding a measure of intrinsic alertness (basic attentional intensity) [19]. In the second condition, the appearance of the cross was preceded by a warning tone. The latter condition assessed the capability to focus attention on an anticipated event (phasic alertness)[19].

Go-Nogo

Motor response times were obtained in context of a selective response task, in which patients had to press a button in response to the appearance of a predefined critical stimulus, while a response had to be avoided in case of the appearance of a noncritical stimulus. The test addresses selective attention and response inhibition.

Divided Attention

Additional motor response times were assessed during a task in which attention had to be allocated simultaneously to visual and auditory stimuli. Patients were required to press a button as soon as moving crosses on the screen formed a square, and when a sequence of alternating high and low-pitch tones was broken as the same tone appeared twice in sequence. It should be noted that this test also addresses working memory and cognitive flexibility due to the fact that the putative occurrence of response cues during the test (square, same tone twice in a row) needs to be continuously monitored and compared to the memorized response cues, predefined during the test instructions.

Verbal and nonverbal fluency

The Regensburger Wortschatz-Test (english: lexical test; RWT) [20] is a test measuring verbal fluency and divergent thinking. Several time-restricted verbal tasks (one-minute) were included. In a first task, patients had to generate as many words as possible, beginning with a specific letter (phonematic fluency). Subsequently, words had to be generated belonging to a specific category (semantic fluency). In addition, patients were required to produce words, switching back and forth between two predefined first letters and between two predefined categories (see Additional file 1: Supplement 1). As such, the latter tasks involved an additional emphasis on working memory functioning.

The Five-Point-Test (FPT) [21] was used for the assessment of nonverbal fluency. Patients were required to draw as many different patterns as possible on a piece of paper by connecting dots within several squares during a three-minute time span. As was the case in the RWT, working memory functioning may be regarded as a crucial element to solve this test as patients had to ensure not to repeat any pattern. Additional information on all test parameters can be reviewed in Additional file 1: Supplement 2.

Derivation of sensitivity and specificity estimates

Data was processed by means of SPSS 20.0 (IBM). In order to determine sensitivity and specificity of the short BRB, several parameters were derived: Sensitivity describes the ratio of patients identified as cognitively impaired by both the short BRB and the extensive test battery (true positives), whereas specificity is the ratio of patients identified as cognitively unimpaired by the short BRB and the extensive test battery (true negatives). Performance on any given test was regarded as impaired if it involved a percentage rank (PR) < 16, based on age-corrected normative data of each test. Confidence intervals (95 %; CI) were calculated according to an efficient-score method, corrected for continuity [22].

Calculation of Parameters

Sensitivity and specificity were derived for several configurations. First and foremost, the whole screening was matched with the whole extensive test battery, a patient being considered impaired if one test parameter indicated cognitive impairment (PR < 16).

Furthermore, sensitivity and specificity were also calculated for each subtest of the BRB (SRT, SDMT, PASAT) in comparison to the whole extensive test battery. Again, a patient was considered impaired if at least one test parameter indicated cognitive impairment (PR < 16).

Finally, the three different cognitive domains addressed by the three subtests of the BRB were considered. The three cognitive domains were conceptualized as memory (SRT), speed (SDMT) and working memory and attention (PASAT). Tests of the extensive procedure were assorted to these domains, as displayed in Table 2. Sensitivity and specificity of a respective BRB subtest in predicting impairment in a corresponding domain of the extensive procedure were then determined. A domain of the extensive procedure was considered impaired if scores in any test belonging to that domain fell below the threshold of PR <16. For further information on test parameters, see Additional file 1: Supplement 2.

Results

Considering the extensive testing procedure, 72 patients (57.1 %) showed cognitive deficits, whereas in the short version of the BRB, 75 patients (59.5 %) were identified as cognitively impaired. When matching the whole of the screening (SRT, SDMT, PASAT) with the gold standard of the extensive test battery, sensitivity was 77.8 % and specificity was 64.8 % (Table 3).

Screening subtests were also individually matched with the whole of the extensive test battery (Table 3), resulting in lower sensitivity values (38 % for the SRT, 41.7 % for the PASAT and 43.8 % for the SDMT), but increasing specificity values (81.5 % for the SRT, 87.0 % for the PASAT and 94.4 % for the SDMT).

Finally, obtained estimates of sensitivity and specificity of the three subtests of the screening matched with their respective domains from the extensive test battery are displayed in Table 4. Sensitivity ranged from 49.1 % in the working memory domain (PASAT) to 60.0 % in the

Table 2 Composition of cognitive domains in the screening and the extensive test battery.

Domain	Equivalent in screening	Equivalent in extensive test battery
Memory	SRT	CVLT
Speed	SDMT	TAP – ALTAP – GOWMS-R-DS forwardWMS-R-BS forward
Working memory	PASAT	TAP – GAWMS-R-DS backward WMS-R-BS-backwardFPTRWT

SRT: Selective Reminding Test; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test; CVLT: California Verbal Learning Test; TAP: test of attentional performance; AL: Alertness: GO: Go-NoGo; GA: Divided Attention; WMS-R: Wechsler Memory Scale – Revised; DS: digit span; BS: block span; FPT: Five-Point-Test; RWT: Regensburger Wortschatz Test

Table 3 Performance of screening-subtests (single and combined)

	Sensitivity (95 % CI)	Specificity (95 % CI)
SRT	38.36 % (27.44 % - 50.51 %)	81.48 % (68.13 % - 90.30 %)
SDMT	43.84 % (32.41 % - 55.91 %)	94.44 % (83.66 % - 98.55 %)
PASAT	41.67 % (30.35 % - 53.88 %)	87.04 % (74.48 % - 94.19 %)
SRT +SDMT + PASAT	77.78 % (66.15 % - 86.39 %)	64.81 % (50.55 % - 76.97 %)

CI: Confidence Interval; SRT: Selective Reminding Test; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Addition Test

memory domain (SRT), and a corresponding estimate in the speed domain of 52.9 % (SDMT). Specificity was considerably higher, ranging from 81.5 % in the memory domain to 89.5 % in the speed domain, with the memory domain falling in between these two with a value of 84.9 %.

In sum, consistent estimates above chance level for both, sensitivity and specificity, were only reached in case of the first approach, i.e. matching the whole of the screening with the extensive test battery. While utilizing individual screening subtests increased specificity, this approach involved considerably attenuated sensitivity. Further information regarding the number of cognitively impaired patients in each subtest of the screening as well as each cognitive domain in the extensive testing procedure can be reviewed in Additional file 1: Supplement 3.

Discussion

A thorough diagnosis of cognitive deficits in MS-patients is a time- and resource-consuming process consisting of a large number of neuropsychological test procedures. In clinical practice, where time for excessive assessments is sparse, such a thorough diagnosis is often not feasible. Therefore, short assessment methods could essentially improve the diagnostic process.

In the current study, MS-patients completed both, an economic screening session by means of a brief version of the BRB, as well as an extensive diagnostic procedure closely adhering to established standards of an extensive testing in MS[5,6]. The proportion of patients who were identified as displaying cognitive deficits was relatively similar between the screening (59.5 %) and the extensive procedure (57.1 %). As such, it resembles common estimates, according to which neuropsychological deficits occur in about 40-65 % of MS-patients [1].

Table 4 Performance of screening-subtests in respective extensive test battery domains

	Sensitivity (95 % CI)	Specificity (95 % CI)
SRT	60.00 % (42.21 % - 75.65 %)	81.52 % (71.78 % - 88.57 %)
SDMT	52.94 % (38.60 % - 66.84 %)	89.47 % (79.79 % - 95.02 %)
PASAT	49.06 % (35.25 % - 63.00 %)	84.93 % (74.21 % - 91.88 %)

CI: Confidence Interval; SRT: Selective Reminding Test; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Addition Test

Matching the whole of the short version of the BRB with the whole extensive testing procedure resulted in a sensitivity of 77.8 % and a specificity of 64.8 %. In the current work, this matching constellation was the only one which produced consistent estimates of sensitivity and specificity above chance level. In contrast, a clearly different pattern of results emerged when BRB subtests were individually matched with results of the entire extensive testing procedure. Here, sensitivity was lower (38.7 % to 43.8 %), whereas specificity was somewhat increased (81.5 % to 94.4 %). Sensitivity estimates for the individual subtests of the short version of the BRB referring to the respective domains of the extensive testing procedure resulted in only marginally increased sensitivity (49.1 %-60.0 %) and approximately equal specificity (81.5 %-89.5 %). While this common pattern of elevated specificity relative to sensitivity on the subtest-level is compatible with previous reports by Portaccio et al. [12], overall estimates of sensitivity and specificity obtained in the current study are considerably lower than those reported by the latter authors.

While Portaccio et al. [12] reported specificity estimates of 84 % for the short version of the BRB, in the current study, 64.8 % were obtained. The same pattern holds for sensitivity, where Portaccio et al. [12] reported 94 %, whereas in the current study, 77.8 % were obtained. As previously indicated, in the study by Portaccio et al., [12] there was a considerable overlap of tests included in the short screening version of the BRB on the one hand, and the procedure which was implemented to derive reliable information about the actual presence of cognitive deficits on the other hand. Similar classification patterns between the shortened version of the BRB and the more extensive procedure in the latter work might hence have been the result of overestimation. In support of this assumption, estimates of the current work, which were based on an extensive diagnostic procedure completely independent from the screening, were considerably lower.

While estimates of specificity and sensitivity in the current work were lower than those of Portaccio et al., [12] it is remarkable that despite the fact that a relatively independent diagnostic procedure was implemented, estimates were still reasonable, when the screening was considered as a global predictor. In particular the important parameter *sensitivity*, representing the proportion of patients adequately identified as cognitively impaired by the screening, showed a reasonable estimate. While adequacy in identifying patients without cognitive deficits, reflected by specificity, was somewhat lower, it may be argued that the latter group of patients would probably be examined by an extensive procedure subsequently by default in context of routine clinical practice. In that case, a false positive result would yield a subsequent extensive examination to verify the screening result. The fact that the screening actually identified *more* patients as cognitively impaired than the extensive testing procedure further underlines its usefulness for a short assessment and its appropriateness as a screening tool. In sum, the current findings may be regarded as complementing previous suggestions by Portaccio et al., [12] as they provide further support for the utility of the short version of the BRB as a valid screening tool. Nevertheless, it needs to be emphasized that according to the current findings, the feasibility is only given when the screening is regarded as a global indicator.

Another noteworthy aspect of the current study concerns the usefulness and necessity of the application of the PASAT in future diagnostic procedures. In the past, it has often been pointed out that the PASAT is somewhat flawed since it requires a certain amount of mathematical ability [23]. It also acts as a potential stressor, since patients are required to keep up with the pace of the number reading [24]. Therefore, the question has been raised whether to completely abstain from using it in test batteries and instead favouring the SDMT, which is generally better accepted by patients [25]. The current study shows that, even though the SDMT is slightly superior to the PASAT in terms of specificity, each test by itself has a fairly low sensitivity. Only combined with each other and the SRT can they reach sufficiently high levels of sensitivity to be deemed as having an adequate predictive value.

In the current study, we decided against implementing a Stroop-Test in addition to the short version of the BRB. On the one hand, executive functions are already being addressed by the PASAT. On the other, a Stroop-Test would significantly lengthen the screening-procedure, [26] which would countermand the aim of an economic screening tool. However, it should be noted that the underlying cognitive constructs of the PASAT are still a matter of debate [23, 24] and that a short test for executive function in MS is still lacking. It is for this last reason that we decided against the BICAMS and for the short BRB in our study. Both approaches require approximately 15 minutes (testing time only) and both consist of three subtests. But even though validation of the BICAMS is currently underway in several countries as a short screening tool in MS [27], we consider the three subtests of the BRB to better cover the width – if not the depth – of neuropsychological constructs possibly affected in MS, since they have the arguable benefit of also assessing executive functions through the PASAT.

While our results are generally compatible with the extant literature and provide an extension with regards to the previous work by Portaccio et al., [12] it should be noted that in the current study, the extensive diagnostic procedure was not implemented on the same assessment occasion as the screening. Consequently, a second appointment had to be scheduled. Relatively decreased specificity and sensitivity estimates may have been affected by these circumstances. On the other hand, it is noteworthy that despite the delay between testing procedures, specificity and sensitivity estimates of the short version of the BRB were still reasonable. However, since stability of cognitive deficits in MS over time is still debated and longitudinal studies in this field of research are scarce, [28] time intervals between screening and extensive testing should be avoided in further research in this area.

Conclusion

In summary, current results show that the suggested short screening tool consisting of the BRB-subtests PASAT, SDMT and SRT is indeed a valid instrument for a time- and cost-efficient first assessment of cognitive deficits in MS-patients when it is regarded as a global indicator.

Additional file

Additional file 1: Supplement 1. Additional information on neuropsychological tests. **Supplement 2.** - Additional information on test parameters. **Supplement 3.** – flow diagram on diagnostic procedures and number of cases (DOC 46 kb)

Competing interests

The current article was supported by Bayer Vital GmbH. Dr. Keune, Dr. Münßinger and Prof. Dr. Oschmann received research support and compensation for activities with Bayer Vital GmbH.

Authors' contributions

SH coordinated the implementation of the study, performed the data analysis and drafted the manuscript. JM helped implement the study and supported the data analytic process. SK helped implement the study. SL and PO participated in the development of the study design and edited the manuscript. PK supported the data analytic process and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

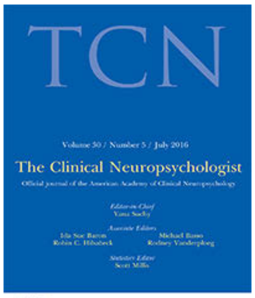
The authors like to express their gratitude to Dr. Uwe Menge for his support in designing the study as well as to Katharina Herzog for contributing to data acquisition and data analysis. The current work was supported by Bayer Vital GmbH.

Received: 28 July 2015 Accepted: 17 November 2015
Published online: 26 November 2015

References

1. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: A review of recent developments. Curr Opin Neurol. 2003;16:283–8.
2. Calabrese P, Penner IK. Neuropsychologische Defizite bei entzündlichen Erkrankungen des ZNS. In: Sturm W, Herrmann M, Münte TF, editors. Lehrbuch der Klinischen Neuropsychologie. 2nd ed. Heidelberg: Spektrum; 2009. p. 672–86.
3. Langdon D. Cognitive impairment in multiple sclerosis – recent advances and future prospects. European Neurological Review. 2010;5:69–72.
4. Langdon DW. Cognition in multiple sclerosis. Curr Opin Neurol. 2011;24:244–9.
5. Benedict RH. Integrating cognitive function screening and assessment into the routine care of multiple sclerosis patients. CNS Spectr. 2005;10:384–91.

6. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). Multiple Sclerosis Journal. 2012;18:891–8.
7. Rao SM and the Cognitive Function Study Group of the National Multiple Sclerosis Society. A manual for the Brief Repeatable Battery of Neuropsychological Tests in multiple sclerosis. Milwaukee, WI: Medical College of Wisconsin.
8. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology. 1991;41:685–91.
9. Sepulcre J, Vanotti S, Hernández R, Sandoval G, Cáceres F, Garcea O, et al. Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. Multiple Sclerosis Journal. 2006;12:187–95.
10. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, Houtchens MK, et al. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Multiple Sclerosis Journal. 2007;13:1004–10.
11. Portaccio E, Goretti B, Zipoli V, Iudice A, Pina DD, Malentacchi GM, et al. Reliability, practice effects, and change indices for Rao's brief repeatable battery. Multiple Sclerosis Journal. 2010;16:611–7.
12. Portaccio E, Goretti B, Zipoli V, Siracusa G, Sorbi S, Amato MP. A short version of Rao's brief repeatable battery as a screening tool for cognitive impairment in multiple sclerosis. Clin Neuropsychol. 2009;23:268–75.
13. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121–7.
14. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis II. Impact on employment and social functioning. Neurology. 1991;41:692–6.
15. Gronwall DM. Paced auditory serial-addition task: A measure of recovery from concussion. Percept Mot Skills. 1977;44:367–73.
16. Niemann H, Sturm W, Thöne-Otto AI, Willmes K. California Verbal Learning Test Manual. Deutschsprachige Adaptation. Frankfurt am Main: Pearson, 2008.
17. Härting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J. Wechsler Gedächtnistest – Revidierte Fassung Manual. Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale. 1st ed. Bern: Huber; 2000.
18. Zimmermann P, Fimm B. Testbatterie zur Aufmerksamkeitsprüfung [Testbattery of Attentional Performance (TAP)] version 2.2. Vera Fimm: Herzogenrath; 2009.
19. Sturm W, Willmes K. On the Functional Neuroanatomy of Intrinsic and Phasic Alertness. Neuroimage. 2001;14:76–84.
20. Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test [lexical fluency test]. Göttingen: Hogrefe; 2000.
21. Regard M, Strauss E, Knapp P. Children's production on verbal and non-verbal fluency tasks. Percept Mot Skills. 1982;55:839–44.
22. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. Stat Med. 1998;17:857–72.
23. Rogers JM, Panegyres PK. Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. J Clin Neurosci. 2007;14:919–27.
24. Fish JD, Archibald CJ. Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis. J Int Neuropsychol Soc. 2001;7:363–72.
25. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Multiple Sclerosis Journal. 2014;20:481–8.
26. Bäumler G. Farbe-Wort-Interferenztest (FWIT) nach J. R. Stroop. Göttingen: Hogrefe; 1985.
27. Benedict RH, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol. 2012;12:55.
28. Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. J Neurol Sci. 2006;245:41–6.



The Clinical Neuropsychologist

ISSN: 1385-4046 (Print) 1744-4144 (Online) Journal homepage: http://www.tandfonline.com/loi/ntcn20

Cognitive screening in Multiple Sclerosis: the Five-Point Test as a substitute for the PASAT in measuring executive function

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ABSTRACT

Objective: The Paced Auditory Serial Addition Test (PASAT) is frequently employed to measure executive functions in patients with Multiple Sclerosis (MS). In the past, the PASAT has often been criticized because of its stressful and demanding requirements. Continuous utilization might also reduce its validity. The Five-Point Test (FPT) by Regard, Strauss, and Knapp ((1982) Children's production on verbal and non-verbal fluency tasks. *Perceptual and Motor Skills, 55*, 839–844.) is a short test of figural fluency which might serve as a substitute. **Method**: 116 patients diagnosed with MS were tested with a short version of the Brief Repeatable Battery (BRB) by Rao and the Cognitive Function Study Group of the National Multiple Sclerosis Society including the PASAT, as well as the FPT. A factor analysis was computed and the frequency of cognitive impairment was calculated for both the original short version of the BRB and the alternative version (involving the FPT). **Results**: In the factor analysis, PASAT and FPT loaded highest on the same factor (two factors were extracted). The estimation of the frequency of cognitive impairment showed that replacing the PASAT with the FPT did not considerably alter the proportion of patients identified as cognitively impaired. **Conclusions**: The FPT proved to be a viable alternative to the PASAT in this study. It may be recommended as a possible replacement in neuropsychological screening of MS-patients with the advantage of avoiding the indicated limitations of the PASAT.

ARTICLE HISTORY
Received 13 April 2016
Accepted 21 September 2016

KEYWORDS
Multiple sclerosis (MS); Paced Auditory Serial Addition Test (PASAT); Five-Point Test (FPT); executive functions; Brief Repeatable Battery (BRB); figural fluency; design fluency

Introduction

Cognitive deficits in patients with Multiple Sclerosis (MS) are common, with incidence rates ranging from 40 to 60% (e.g. Bobholz & Rao, 2003; Hansen et al., 2015). Along with ambulatory problems, neurological dysfunctions, depression, and fatigue, they are among the most debilitating symptoms of MS (Amato, Zipoli, & Portaccio, 2006; Burschka et al., 2012; Chiaravalloti & DeLuca, 2008; Hofstadt-van Oy, Keune, Muenssinger, Hagenburger, & Oschmann, 2015; Keune et al., 2015). Disease onset time is often in a stage of life that overlaps with early adulthood, vocational training, and quite generally finding one's own place in the world. Therefore, the diagnosis of MS and its associated deficits in routine examinations of

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affected patients is of great significance. However, due to the limited resources in the health care sector, extensive neuropsychological testing of each MS-patient is often not feasible (Hansen et al., 2015). This conflict is especially comprehensible when considering the guidelines of the Minimal Assessment of Cognitive Function in Multiple Sclerosis group (MACFIMS; Benedict et al., 2002), whose suggested elaborate testing procedures easily take up two hours or more.

In contrast, short screening tools exist which allow the clinician to form an educated assumption on the presence or absence of cognitive deficits. Since such a screening is far from comprehensive, the clinician may still schedule an extensive testing procedure in case of a positive screening result. Research on cognition in (BICAMS) has lately shown the practical feasibility of such an economic approach to neuropsychological assessment in clinical practice. The Brief International Cognitive Assessment for MS is an extremely short tool which is currently being validated multi-nationally (Benedict, 2005; Benedict et al., 2012; Langdon et al., 2012). Utilizing three subtests, it assesses attention as well as verbal and nonverbal memory, however, arguably neglecting executive functions (McNicholas & McGuigan, 2016).

Another approach relies on the Brief Repeatable Battery (BRB) by Rao and the Cognitive Function Study Group of the National Multiple Sclerosis Society (1990). Hansen et al. (2015), elaborating on research by Portaccio et al. (2009), showed that a short form of the BRB is suitable as a screening tool, since it reaches acceptable values of sensitivity and specificity compared to the gold standard of an extensive testing procedure. This screening tool includes three tests, namely the Paced Auditory Serial Addition Test (PASAT) addressing information processing speed and working memory (Gronwall, 1977; Strauss, Sherman, & Spreen, 2006), the Symbol Digit Modalities Test (SDMT) addressing psychomotor speed and attention (Rao and the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990), and the Selective Reminding Test (SRT) as a measure of long-term and consistent verbal memory (Buschke & Fuld, 1974). These three procedures address the breadth – if not the depth – of neuropsychological constructs, covering attention, memory, and executive function.

In the past, it has often been argued that the PASAT may not be suitable as a short screening tool, since it remains ambiguous which underlying neuropsychological constructs are addressed specifically. Both attentional processes in the form of information processing speed (Forn, Belenguer, Parcet-Ibars, & Avila, 2008) as well as executive function in the form of working memory (e.g. Rogers & Panegyres, 2007) are reflected by performance on the PASAT. The PASAT requires a participant to perform pairwise additions of auditorily presented numbers. Although this clearly brings to mind associations with N-back-tasks or other classical working memory paradigms, other mental abilities such as arithmetic skills or calculation speed may have a significant influence on the outcome and may therefore be considered as confounding factors (Sandry, Paxton, & Sumowski, 2016). Further, clinical experience shows that regardless of whether cognitive impairment is present or not, patients may show difficulties in accepting the PASAT. It is often perceived as being stressful and demanding (Fisk & Archibald, 2001), and may be declined outright.

Consequently, the question arises whether the PASAT could be replaced by another test without loosing the predictive value of the short form of the BRB. Other authors proposed to completely abstain from employing the PASAT without substitution (Sonder, Burggraaff, Knol, Polman, & Uitdehaag, 2014). However, it has been shown that such an approach may dramatically reduce the predictive value of the screening (Hansen et al., 2015). In this light, simply omitting the PASAT does not seem feasible. However, it might be possible to substitute the PASAT with another diagnostic procedure involving comparable properties.

Referring to the question which test could replace the PASAT as a measure of executive function in a short screening tool, several alternatives may be available. In the past, the Stroop-Test (Arnett et al., 1997), the Wisconsin Card Sorting Test (Parmenter et al., 2007), the Sorting subtest of the Delis–Kaplan Executive Function System (Benedict et al., 2002; Parmenter et al., 2007), and variants of the Tower of London or Tower of Hanoi Test (Arnett et al., 1997; Foong et al., 1997) have been used for the diagnosis of executive functions in MS. However, each of these entails a lengthy testing procedure as well as complex preparation procedures or material. Therefore, none of them appears particularly suitable to replace the PASAT in a short screening.

Fluency, on the other hand, can be tested with little effort and is frequently deficient in MS-patients (Henry & Beatty, 2006). The Five-Point Test (FPT) is a short and simple test for measuring figural fluency as an executive function (Regard, Strauss, & Knapp, 1982). It has recently been validated (Goebel, Fischer, Ferstl, & Mehdorn, 2009) and the fact that norms not only exist for fluency-measures but also for strategy use in item generation as well as perseverations makes the FPT preferable in comparison to verbal-fluency measures. The consideration of strategies applied by the patient makes the FPT a particularly valuable measure of executive functioning in the context of a fluency task.

In the FPT, the patient has to connect five dots aligned as on a dice (see Figure 1 for a display of the test paradigm). The outcome measure is the number of unique patterns created within three minutes. Besides figural fluency as a measure of executive function, this test also relies on psychomotor speed as well as on visual–spatial and visual-constructive abilities (Strauss et al., 2006). In comparison to the PASAT, instructions and implementation of the FPT appear relatively simple. Just like the PASAT, this task takes three minutes and the FPT is therefore well suited to complement a short screening. Moreover, in contrast to the PASAT, to our knowledge there have been no reports on participants' reactance to this test in the current literature.

The procedure of the FPT is quite similar to that of the Ruff Figural Fluency Test (RFFT; Ruff, Light, & Evans, 1987), which is indeed a variation on the FPT. According to the extant literature, it assesses planning abilities as well as attention, but also general intelligence (Lezak, Howieson, Bigler, & Tranel, 2012). However, the FPT is shorter and easier to execute than the RFFT. Though the RFFT is probably the more established measure among these two, its multiple test conditions have been argued to involve some redundancy (Strauss et al., 2006). Furthermore, the assessment of strategy use in the RFFT remains a matter of debate, whereas

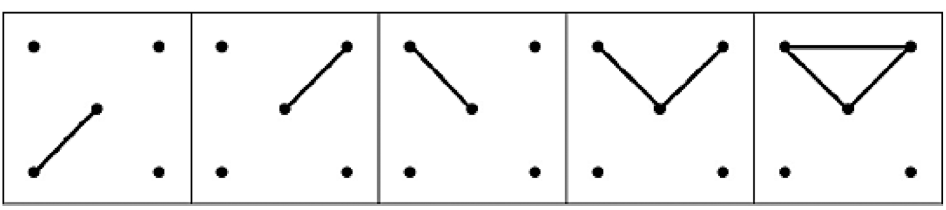


Figure 1. Examples for strategy use in the Five-Point Test.
Notes: The second and third items are based on a rotation of the first item, thus counting as created by the rotational strategy. In the fourth and fifth item, exactly one line is added to the respectively previous design, thus counting as created by the addition strategy. For more information on scoring in the FPT, see Appendix 2. The figure was designed by the authors of this study.

strategy use can be calculated reliably and with relative ease in the FPT (Goebel et al., 2009). Based on these considerations, we decided to favor the FPT over the RFFT in the current study.

At first glance, the comparison of test paradigms of the PASAT and the FPT suggests that the common cognitive function addressed is information processing speed, as both tests involve time constraints. However, as indicated above, the PASAT also requires the recruitment of executive functions (working memory) in order to solve the pairwise additions, while numbers are continuously played. The FPT, besides addressing speed, also considers executive functioning due to the fact that a strategy parameter is derived when the test is scored. This parameter considers methodological processing and the execution of planned patterns during the completion of the task, as outlined in detail in the methods section of the current work. The FPT and the PASAT hence overlap in two important domains, i.e. information processing speed and executive function.

The purpose of the current work was to evaluate whether the FPT could serve as a substitution for the PASAT. If so, it might solve the issue of patients' potential reactance to the PASAT while retaining a measure of executive functioning in the screening.

To address this issue, we examined the extent of variance common to the variables of the three screening subtests (PASAT, SDMT, SRT) and the FPT. A factor-analytic approach involving the screening-subtests and the FPT was employed. Further, it was evaluated whether the proportion of patients identified as cognitively impaired by the commonly employed short version of the BRB (PASAT, SDMT, SRT) would remain relatively stable if the FPT variables were to replace the PASAT.

We expected the FPT and PASAT to share a considerable amount of variance because in both tests, executive functions are among the cognitive domains which are addressed. Following this argument, both tests might be interchangeable in the screening, which would be suggested by a common underlying factor structure. By the same reasoning, an approximation of the proportion of patients with cognitive deficits as identified by the original screening was expected for the alternative version involving the FPT.

Methods

The short version of the BRB, i.e. the SDMT, PASAT, and SRT as well as the FPT were administered to 116 MS-outpatients at the Department of Neurology, Klinikum Bayreuth GmbH, Germany during the routine clinical process. Testing was conducted by highly practiced psychologists specialized in neuropsychology. Inclusion criteria involved a verified MS-diagnosis (McDonald et al., 2001) and an age range between 18 and 75 years. Patients were not eligible for inclusion if they had severe motor or visual impairments that interfered with cognitive testing or were currently experiencing a clinical exacerbation. They were also not included if they currently received cortisone injections, had received such medication during the last four weeks, or suffered from neurological illnesses other than MS. A flow diagram detailing patient recruitment can be reviewed in Appendix 2. All participants provided written informed consent prior to study entry. The study was approved by the ethics committee of the University of Bayreuth, Germany. Demographics and MS-relevant parameters of the sample can be reviewed in Table 1.

Table 1. Demographical and clinical characteristics of the sample.

	RR-MS	SP-MS	Whole sample
n (%)	90 (77.6)	26 (22.4)	116 (100)
Mean age (*SD*)	40.8 (11.8)	50 (6.8)	42.8 (11.5)
Female sex (%)	59 (65.6)	18 (69.2)	77 (66.4)
Education			
0–9 years (%)	30 (33.3)	15 (57.7)	45 (38.8)
10–12 years (%)	33 (36.7)	7 (26.9)	40 (34.5)
13+ years	27 (30.0)	4 (15.4)	31 (26.7)
Median EDSS (*SD*)	2.0 (1.3)	4.0 (1.4)	2.5 (1.7)
Mean Disease Duration (*SD*)	9.0 (7.3)	16.5 (10.3)	10.5 (8.5)

Note: EDSS = Expanded Disability Status Scale, RR = Relapsing-remitting, SP = Secondary Progressive, MS = Mulitple Sclerosis, *SD* = Standard Deviation.

Applied neuropsychological procedures

The BRB as conceived by Rao and the Cognitive Function Study Group of the National Multiple Sclerosis Society, (1990) originally consists of five tests. In its short form as applied by Portaccio et al. (2009) and Hansen et al. (2015), three of its original tests remain.

The PASAT addresses information processing speed and working memory (Strauss, Sherman, & Spreen, 2006). Several variants of the PASAT exist. In the variant employed in the BRB, an audio recording of 60 numbers is played to the patient with an interstimulus-interval of three seconds. The patient is instructed to add each currently presented number to the one immediately preceding it and to name the result. The performance score is the number of correct calculations.

The SDMT assesses information processing speed and attention (Smith, 1982). Patients are required to verbally pair numbers and symbols according to a fixed pattern, the outcome score being the amount of pairings correctly solved within 90 s.

The SRT involves the presentation of a maximum of six trials of a 12-item word list, in which the examiner only presents those words not recalled on the immediately preceding trial. Presentation is discontinued once a patient recalls all words of the list on two consecutive trials (Buschke & Fuld, 1974). The test yields two parameters, which are long-term storage and consistent long-term-retrieval (CLTR). A word is assumed to enter LTS if it is recalled on two consecutive trials. If it is not reported on consecutive trials, it is then assumed that the patient failed to retrieve it. Only if a word is recalled consistently until the last trial, it will be scored under CLTR.

Additionally, the FPT was included (Regard et al., 1982). It assesses figural productivity and flexibility, i.e. cognitive functions associated with frontal brain areas (Goebel, Atanassov, Köhnken, Mehdorn, & Leplow, 2013; Goebel et al., 2009; Tucha, Aschenbrenner, Koerts, & Lange, 2012). Patients are required to draw as many different patterns as possible on a paper. On this work sheet, 40 contiguous identical squares are arranged in a 5 x 8 array, each square consisting of five symmetrically arranged dots. Patients are instructed to connect a minimum of 2 dots and a maximum of 5 dots to produce as many unique designs as possible during a three-minute time span. Examples for such designs can be seen in Figure 1. If a patient fills the final square on the work sheet before the three minutes have elapsed, a second sheet is handed out and the first sheet is placed within sight. No patients in this study required more than two work sheets.

Patients are explicitly instructed not to repeat any items. The outcome measure is the number of unique, correct items produced. A repetition score is calculated by dividing the number of repetitions by the number of produced items (not counting errors), yielding an index of flexibility.

As a further measure particularly relevant for executive functioning, use of strategies on the FPT may be assessed (Goebel et al., 2009). It has been shown that healthy subjects often produce several items from one design by rotating it. This procedure leads to a removal of cognitive load, reduces the number of repetitions, and increases the overall number of produced items. Another strategy is to build upon a simple design by further differentiating the pattern from item to item. Here, the outcome measure is the number of items produced using one of the strategies mentioned above, divided by the overall number of unique, correct items produced. An example for the above-mentioned strategies can be found in Figure 1. Evaluation of individual test results requires some practice by the examiner but can otherwise be executed within mere minutes, depending on the number of items drawn by the patient. For further information on the calculation of parameters in the FPT, see Appendix 1.

In sum, the FPT yields three parameters closely associated with executive functions. The first one measures productivity as well as operational speed (FPT-Productivity), the second assesses strategy use and methodical approach (FPT-Strategies). A third parameter is the relative amount of repetitions as a measure of flexibility (FPT-Repetitions). Finally, it should be noted that due to the explicit instruction that each produced design needs to be unique, patients are required to engage executive functions due to the monitoring and review process inherent in the task.

Statistical analyses

All calculations were executed with SPSS 20.0.

First, descriptive, exploratory two-sided Pearson correlations for all cognitive parameters were computed. Subsequently, an exploratory factor analysis involving the outcome measures of PASAT, SDMT, SRT-LTS, SRT-CLTR, FPT-Productivity, FPT-Repetitions, and FPT-Strategies was implemented in order to evaluate their underlying factor structure. To assess the suitability of the data for the factor analysis, the Bartlett-test as well as the Kaiser–Meyer–Olkin-criterion were applied.

Finally, it was examined whether replacing the PASAT with the FPT in the screening affected the proportion of patients identified as cognitively impaired. It has repeatedly been shown that the original short version of the BRB (involving the PASAT) displays sufficient sensitivity and specificity relative to a gold standard (Hansen et al., 2015; Portaccio et al., 2009). The current study focused on an analysis across the two versions of the screening (involving PASAT vs. involving FPT). While this approach is methodologically limited compared to the implementation of a gold standard (i.e. administration of an extensive neuropsychological battery), it is still informative with regard to the qualities of the alternative screening, relative to the original.

For both testing procedures, the performance of a patient scoring ≤PR 15 (equal to or lower than a percentage rank of 15) on any test was considered “impaired”. This equals one

Table 2. Descriptive correlations.

	PASAT	SDMT	SRT-LTS	SRT-CLTR	FPT-Prod	FPT-Strat
SDMT	.577**					
SRT-LTS	.197*	.346**				
SRT-CLTR	.235*	.341**	.870**			
FPT-Productivity	.517**	.581**	.238**	.272**		
FPT-Strategies	.399**	.354**	.057	.100	.538**	
FPT-Repetitions	−.263**	−.434**	−.238*	−.301**	−.329**	−.315**

Notes: $n = 116$. Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Selective Reminding Test (SRT), Long-Term Storage (LTS), Consistent Long-Term Retrieval (CLTR), Five Point Test (FPT), Productivity (Prod), Strategies (Strat).

*$p < .05$; **$p < .01$.

standard deviation below the mean and can be considered as a liberal cut-off value when screening for cognitive impairment (Fischer et al., 2014). Normative data for all BRB-subtests were taken from a study by Scherer, Baum, Bauer, Göhler, and Miltenburger (2004). Normative data for the three FPT-scores were taken from Goebel et al. (2009). Please refer to Appendix 1 for further information on the calculation of parameters in the FPT.

Results

Intercorrelations

Results of the descriptive intercorrelations are displayed in Table 2.

Concerning the PASAT, highly significant correlations were found with SDMT ($r = .577$) as well as FPT-Productivity ($r = .517$) and FPT-Strategies ($r = .399$) scores (all p-values < .01). Correlations with SRT-LTS ($r = .197$) and SRT-CLTR ($r = .235$) were somewhat lower, but still significant (all p-values < .05). A negative correlation was found for PASAT and FPT-Repetitions ($r = −.263$, $p < .01$). A similar pattern could be observed for the SDMT which also showed highly significant correlations with FPT-Productivity ($r = .581$) and FPT-Strategies ($r = .354$, all p-values < .01). The two SRT-scores (SRT-LTS and SRT-CLTR) correlated highly with each other ($r = .870$, $p < .01$), and negatively with the FPT-Repetition score ($r = −.238$, $p < .05$ and $r = .301$, $p < .01$, respectively).

Factor analysis

To further analyze the relation of PASAT and FPT, a principal factor analysis with promax rotation was employed to explore the underlying factor-structure of the parameters. The structural matrix of the rotated solution can be reviewed in Table 3. It included the z-transformed outcome measures of the PASAT, the SDMT, the SRT-LTS, and SRT-CLTR as well as the FPT-Productivity, FPT-Strategies, and FPT-Repetition-scores. The Bartlett-test was highly significant and the Kaiser–Meyer–Olkin-criterion reached a value of .709, which can be considered reasonable. Both results point to the suitability of the data for executing a factor analysis. Two factors with eigenvalues greater than 1 accounted for 67.02% of variance. (Factor 1: 45.39%, Factor 2: 21.63%). Correlations of variables with factors suggested that the first component reflected processes of speed, working memory, and strategy, with PASAT ($r = .761$), SDMT ($r = .791$) as well as FPT-Productivity ($r = .826$) and FPT-Strategies ($r = .729$) showing the greatest factor loadings. The second component reflected verbal memory, as SRT-LTS

Table 3. Structural matrix of the factor analysis.

	Component	
	1	2
PASAT	.761	.232
SDMT	.791	.422
SRT-LTS	.267	.956
SRT-CLTR	.314	.955
FPT-Productivity	.826	.263
FPT-Strategies	.729	.011
FPT-Repetitions	−.568	−.360

Notes: *n* = 116.
Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Selective Reminding Test (SRT), Long-Term Storage (LTS), Consistent Long-Term Retrieval (CLTR), Five Point Test (FPT). Values reflect correlations between variables and factors of the rotated solution. Shaded components signify inclusion in the respective factor.

Table 4. Diagnostic congruency of the implemented screening procedures.

		SDMT + SRT-LTS + SRT-CLTRFPT-Productivity + FPT-Strategies			
		impaired	unimpaired		
SDMT + PASAT + SRT-LTS + SRT-CLTR	Impaired	62	7	69	Congruency N impaired 89.9%
	Unimpaired	11	36	47	Congruency N unimpaired 76.6%
		73	43	116	

Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Selective Reminding Test (SRT), Long-Term Storage (LTS), Consistent Long-Term Retrieval (CLTR), Five Point Test (FPT).
Notes: Number of patients (N) with impaired/unimpaired results on the screening involving the original approach (SDMT, SRT and PASAT) and involving the alternative approach (SDMT, SRT, FPT-Productivity and FPT-Strategies). Out of N = 69 patients judged impaired on the original approach, 62 patients were judged impaired on the alternative assessment (congruency N impaired = 89.9%). Out of the total of N = 47 patients judged as unimpaired according to the original approach, N = 36 were judged in the same way on the alternative approach (congruency N unimpaired = 76.6%).

(r = .956) and SRT-CLTR (r = .955) showed the highest loads. The FPT-Repetition score was not associated with any of these factors and was therefore discarded in the following analysis.

Prevalence estimation

Finally, estimates of the prevalence of cognitive impairment in both versions of the screening were derived to determine diagnostic congruency of the two screening procedures. The correspondent cross-tabulation is displayed in Table 4. The first approach consisted of the classical screening with the BRB-subtests PASAT, SRT, and SDMT. As validity of this screening has been firmly established (Hansen et al., 2015; Portaccio et al., 2009), it was used for the estimation of the frequency of cognitive deficits in the sample. In the second approach, the PASAT was replaced by the two parameters of the FPT which loaded highly on the same factor as the PASAT, namely FPT-Productivity and FPT-Strategies.

By means of the original version of the screening, 69 out of 116 patients (59.5%) were identified as cognitively impaired. Out of these 69 patients, the alternative test combination of SRT, SDMT, FPT Productivity, and FPT Strategies identified 62 patients as cognitively impaired, resulting in a congruency of 89.9%. In total, the alternative approach identified 73 patients as cognitively impaired (62.9%). Thus, frequencies of impairment were comparable for both screening approaches. Concerning the identification of unimpaired patients, congruency was somewhat lower, but reached a reasonable value with 76.6%. Accuracy, i.e. the proportion of all tests of the alternative approach that identified patients according to the original version of the screening reached an estimated value of 84.5% and can be considered good.

Discussion

The foremost aim of the current study was to answer the question whether the FPT could be established as a possible alternative to the PASAT in a neuropsychological screening for MS-patients. Taking into account the immense strain, the PASAT may put on patients (Fisk & Archibald, 2001; Sonder et al., 2014), as well as putative concerns about its underlying constructs (Rogers & Panegyres, 2007), it may be appropriate to consider alternative tests as possible replacements.

It has been argued that screening for cognitive dysfunction in MS should always include a test of executive function (Chiaravalloti & DeLuca, 2008) and following this rationale in the current study, we examined the FPT as a potential alternative to the PASAT. The FPT appears feasible since tests of figural fluency are often applied as measures of executive or frontal-lobe function in clinical practice (e.g. Benton & Hamsher, 1989; Jason, 1985; Regard et al., 1982). While performance on the FPT also reflects processing speed, since the test is time-constrained, it is important to note that specific parameters can be derived which are directly linked to executive function, i.e. the use of strategies, as reflected in the FPT-Strategies parameter of the current work (Goebel et al., 2009). Test performance further depends on visual-spatial and visual-constructive abilities (Strauss et al., 2006). Instructions of the FPT are relatively easy to communicate and testing-time alone takes up three minutes – exactly as with the PASAT. With a certain amount of practice, evaluation of results can also be done within a few minutes. The FPT is thus hardly any more time-consuming than the PASAT.

Underlying factor structure of PASAT and FPT performance

Our descriptive analysis by means of intercorrelations of test parameters indicated that PASAT and FPT had common variance. Based on this prerequisite, a factor analysis including all test parameters was implemented. Two factors with eigenvalues greater 1 emerged. The first included PASAT and SDMT as well as FPT-Productivity and FPT-Strategies, supporting our assumption that both PASAT and FPT address a common underlying construct. The observation that the SDMT also showed a high loading confirms that processing speed is a constituent of this factor. An additional parameter was derived, i.e. FPT-Strategies, which conceptually implies a close relation to executive functioning. As the latter parameter also loaded high on the first factor, 'speed and strategy' appears to represent an appropriate label. Notably, the PASAT also addresses working memory functioning. To make the nature of this factor more comprehensible in context of the current study, we decided to collapse the label to 'speed and strategy', based on the notion that working memory functioning is essentially a prerequisite for strategy use. Functions reflected by this factor are predominantly mediated by frontal brain areas. They also rely heavily on cortico-cortical connectivity, which is often found deficient in MS and may be associated with white-matter lesions (Fisk & Archibald, 2001). In sum, the emergence of this 'speed and strategies' factor is in support of our hypothesis that FPT and PASAT share an underlying factor structure of relevance for executive functioning. This may be regarded as compatible with our suggestion that the

FPT might serve as a suitable replacement of the PASAT in the context of a short cognitive screening.

FPT-Repetitions did not load high on any single factor. Neither did the latter parameter comprise a factor of its own in our analysis. While the parameter might be suggested to provide qualitative, descriptive information for an examiner when reviewing a single case profile, it was thus discarded from any further analysis.

Prevalence estimates and diagnostic congruency of a screening involving the FPT

Following the confirmation of our original hypothesis by the factor analysis, i.e. that PASAT and FPT measure related constructs associated with executive function, estimated frequencies of cognitive impairment of the suggested alternative screening and the original approach were compared. To this end, it was tested whether the quality of the alternative screening (SRT, SDMT, FPT) in identifying cognitively affected patients would resemble the one of the original short screening (Portaccio et al., 2009; SRT, SDMT, PASAT). Results revealed that 89.9% of patients identified as cognitively impaired by the original screening were also identified by the alternative version involving the FPT. The number of patients congruently identified as unimpaired by both screenings was reasonable, albeit somewhat lower (76.6%). Overall accuracy was good with a value of 84.5%. As displayed in Table 4, the alternative screening involving the FPT identified somewhat more subjects as cognitively impaired than the original procedure, yet accuracy was adequate. In sum, these findings imply that the constellation of SRT, SDMT, and FPT represents a reasonable alternative to the original screening. Estimated frequencies of cognitive impairment are similar across screenings, reflecting diagnostic congruency. As particularly the common phenomenon of reactance to the PASAT can be avoided by the new procedure, the screening may be worth to be further explored in the context of routine clinical examination.

Conclusion and limitations

In sum, the FPT seems to have the potential to serve as an alternative to the PASAT in the screening of cognitive functions without decreasing its predictive value. Our results imply that both tests are indeed comparable measures addressing processing speed and executive function

Some limitations should be noted when considering the results of this study and the applicability of the FPT. First, the FPT requires fine motor function, which may be negatively affected as the disease progresses. Some research exists on the influence of motor control on nonverbal fluency measures (Fama et al., 1998; Goebel et al., 2013; Kraybill & Suchy, 2008). Though results are somewhat inconsistent and none of the data pertains to an MS-population, the conclusion can be drawn that fine motor function should at least be controlled for in future studies. This might be achieved by the implementation of e.g. a pegboard-task (Fischer, Rudick, Cutter, & Reingold, 1999). In contrast, the PASAT does not depend on fine motor skills, which probably makes it a better choice for the examination of patients with motor deficits. The fact that the proportion of participants identified as cognitively impaired remained relatively stable, when the PASAT was replaced with the FPT, does not suggest that fine motor deficits were a substantially confounding factor in the current work. However, it cannot be ruled out that the marginal difference, i.e. slightly more patients identified as cognitively impaired based on the screening involving the FPT, might be attributable to this different role of fine motor functions.

By the same reasoning, impaired visual perception may have slightly influenced performance in the FPT. Though we excluded patients with severe visual deficits, future studies should also control for visual impairments on FPT performance.

Furthermore, it is important to highlight that the original screening procedure in our study does not qualify as an extensive test battery and should therefore not be considered as a 'gold standard'. Our reasoning for our comparative approach relies on previous studies by Portaccio et al. (2009) and Hansen et al. (2015) which identified the brief BRB as a sufficiently sensitive screening tool. Nonetheless, interpretation of our convergence analysis between the two approaches (i.e. crosstabulation) has to mainly focus on the observation that both screening procedures generate similar frequencies of impairment. An interpretation regarding general sensitivity and specificity of the two test protocols would be invalid based on the current data. In order to ascertain the predictive value of the alternative screening including the FPT, future studies should compare results with an independent test battery such as MACFIMS (Benedict et al., 2002). This would fulfill the requirements posed to a "gold standard" for cognitive assessment in MS.

Finally, in order to provide a qualitative score for PASAT performance, dyads (Fisk & Archibald, 2001; Gonzalez et al., 2006) might be computed. This would yield the additional advantage of having a direct comparison with qualitative scores from the FPT.

In conclusion, the FPT appears to be a suitable substitute for the PASAT in a cognitive screening for MS-patients. Other than the PASAT, it is well accepted and largely positively received by patients. The FPT could step in as a true alternative to the PASAT. It might positively widen the scope of cognitive assessment in MS. As the results of this study show, it might be a feasible and time-economic solution to the highlighted necessity of also screening for executive dysfunctions.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The current study was supported by Bayer Vital GmbH Germany. Dr. Keune, Dr. Münßinger and Prof. Dr. Oschmann received research support and compensation for activities with Bayer Vital GmbH Germany.

References

Amato, M. P., Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *Journal of the Neurological Sciences, 245*, 41–46.

Arnett, P. A., Rao, S. M., Grafman, J., Bernardin, L., Luchetta, T., Binder, J. R., & Lobeck, L. (1997). Executive functions in multiple sclerosis: An analysis of temporal ordering, semantic encoding, and planning abilities. *Neuropsychology, 11*, 535–544.

Benedict, R. H. (2005). Integrating cognitive function screening and assessment into the routine care of multiple sclerosis patients. *CNS Spectrums, 10*, 384–391.

Benedict, R. H., Amato, M. P., Boringa, J., Brochet, B., Foley, F., & Fredrikson, S., … Langdon, D. (2012). Brief International Cognitive Assessment for MS (BICAMS): International standards for validation. *BMC Neurology, 12*, 55.

Benedict, R. H., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., … Munschauer, F. (2002). Minimal neuropsychological assessment of MS patients: A consensus Approach. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D), 16*, 381–397.

Benton, A. L., & Hamsher, K. D. (1989). *Multilingual aphasia examination*. Iowa City, IA: AJA Associates.

Bobholz, J. A., & Rao, S. M. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Current Opinion in Neurology, 16*, 283–288.

Burschka, J. M., Keune, P. M., Menge, U., Hofstadt-van Oy, U., Oschmann, P., & Hoos, O. (2012). An exploration of impaired walking dynamics and fatigue in multiple sclerosis. *BMC Neurology, 12*, 161–168.

Buschke, H., & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology, 24*, 1019–1025.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology, 7*, 1139–1151.

Fama, R., Sullivan, E. V., Shear, P. K., Cahn-Weiner, D. A., Yesavage, J. A., Tinklenberg, J. R., & Pfefferbaum, A. (1998). Fluency performance patterns in Alzheimer's Disease and Parkinson's Disease. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D), 12*, 487–499.

Fischer, J. S., Rudick, R. A., Cutter, G. R., & Reingold, S. C. (1999). The Multiple Sclerosis functional composite measure (MSFC): An integrated approach to MS clinical outcome assessment. *Multiple Sclerosis, 5*, 244–250.

Fischer, M., Kunkel, A., Bublak, P., Faiss, H. J., Hoffmann, F., Sailer, M., … Köhler, W. (2014). How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? *Journal of the Neurological Sciences, 343*, 91–99.

Fisk, J. D., & Archibald, C. J. (2001). Limitations of the paced auditory serial addition test as a measure of working memory in patients with multiple sclerosis. *Journal of the International Neuropsychological Society, 7*, 363–372.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., … Ron, M. A. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain, 120*, 15–26.

Forn, C., Belenguer, A., Parcet-Ibars, M. A., & Avila, C. (2008). Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT. *Journal of Clinical and Experimental Neuropsychology, 30*, 789–796.

Goebel, S., Atanassov, L., Köhnken, G., Mehdorn, H. M., & Leplow, B. (2013). Understanding quantitative and qualitative figural fluency in patients with Parkinson's disease. *Neurological Sciences, 34*, 1383–1390.

Goebel, S., Fischer, R., Ferstl, R., & Mehdorn, H. M. (2009). Normative data and psychometric properties for qualitative and quantitative scoring criteria of the Five-Point Test. *The Clinical Neuropsychologist, 23*, 675–690.

Gonzalez, R., Miller, S.W., Carey, C. L., Woods, S. P., Rippeth, J. D., Schweinsburg, B. C., … Heaton, R. K. (2006). Association between dyads and correct responses on the Paced Auditory Serial Addition Task (PASAT). *Assessment, 13*, 381–384.

Gronwall, D. M. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44*, 367–373.

Hansen, S., Keune, P. M., Kronhofmann, S., Muenssinger, J., Lautenbacher, S., & Oschmann, P. (2015). Cognitive screening tools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. *BMC Neurology, 15*, 246–252.

Henry, J. D., & Beatty, W. W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia, 44*, 1166–1174.

Hofstadt-van Oy, U., Keune, P. M., Muenssinger, J., Hagenburger, D., & Oschmann, P. (2015). Normative date and long-term test-retest reliability of the triple stimulation technique (TST) in multiple sclerosis. *Clinical Neurophysiology, 126*, 356–364.

Jason, G. W. (1985). Gesture fluency after focal cortical lesions. *Neuropsychologia, 23*, 463–481.

Keune, P. M., Cocks, A. J., Young, W. R., Burschka, J. M., Hansen, S., Hofstadt-van Oy, U., … Oschmann, P., & Muenssinger, J. (2015). Dynamic walking features and improved walking performance in multiple sclerosis patients treated with fampridine (4-aminopyridine). *BMC Neurology, 15*, 171–178.

Kraybill, M. L., & Suchy, Y. (2008). Evaluating the role of motor regulation in figural fluency: Partialing variance in the Ruff Figural Fluency Test. *Journal of Clinical and Experimental Neuropsychology, 30*, 903–912.

Langdon, D. W., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., … Benedict, R. H. (2012). Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Multiple Sclerosis Journal, 18*, 891–898.

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, T. (2012). *Neuropsychological assessment*. New York, NY: Oxford University Press.

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., … Wolinsky, J. S. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of Multiple Sclerosis. *Annals of Neurology, 50*, 121–127.

McNicholas, N., McGuigan, C. (2016). A useful annual review of cognition in relapsing MS is beyond most neurologists – YES. *Multiple Sclerosis Journal*, *22*, 726–728.

Parmenter, B. A., Zivadinov, R., Kerenyi, L., Gavett, R., Weinstock-Guttman, B., Dwyer, M. G., … Benedict, R. H. (2007). Validity of the Wisconsin Card Sorting and Delis-Kaplan Executive Function System (DKEFS) Sorting Tests in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology,* 29, 215–223.

Portaccio, E., Goretti, B., Zipoli, V., Siracusa, G., Sorbi, S., & Amato, M. P. (2009). A short version of Rao's brief repeatable battery as a screening tool for cognitive impairment in multiple sclerosis. *The Clinical Neuropsychologist, 23*, 268–275.

Rao, S. M. , & the Cognitive Function Study Group of the National multiple sclerosis Society. (1990). *A manual for the Brief Repeatable Battery of Neuropsychological tests in multiple sclerosis*. Milwaukee: Medical College of Wisconsin.

Regard, M., Strauss, E., & Knapp, P. (1982). Children's production on verbal and non-verbal fluency tasks. *Perceptual and Motor Skills, 55*, 839–844.

Rogers, J. M., & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. *Journal of Clinical Neuroscience, 14*, 919–927.

Ruff, R. M., Light, R., & Evans, R. (1987). The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology, 3*, 37–51.

Sandry, J., Paxton, J., & Sumowski, J. F. (2016). General mathematical ability predicts PASAT performance in ms patients: Implications for clinical interpretation and cognitive reserve. *Journal of the International Neuropsychological Society, 22*, 375–378.

Scherer, P., Baum, K., Bauer, H., Göhler, H., & Miltenburger, C. (2004). Normalization of the brief repeatable battery of neuropsychological tests (BRB-N) for German-speaking regions. Application in relapsing-remitting and secondary progressive multiple sclerosis patients. *Der Nervenarzt, 75*, 984–990.

Smith, A. (1982). *Symbol digit modalities test*. Los Angeles, CA: Western Psychological Services.

Sonder, J. M., Burggraaff, J., Knol, D. L., Polman, C. H., & Uitdehaag, B. M. (2014). Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Multiple Sclerosis Journal*, *20*, 481–488.

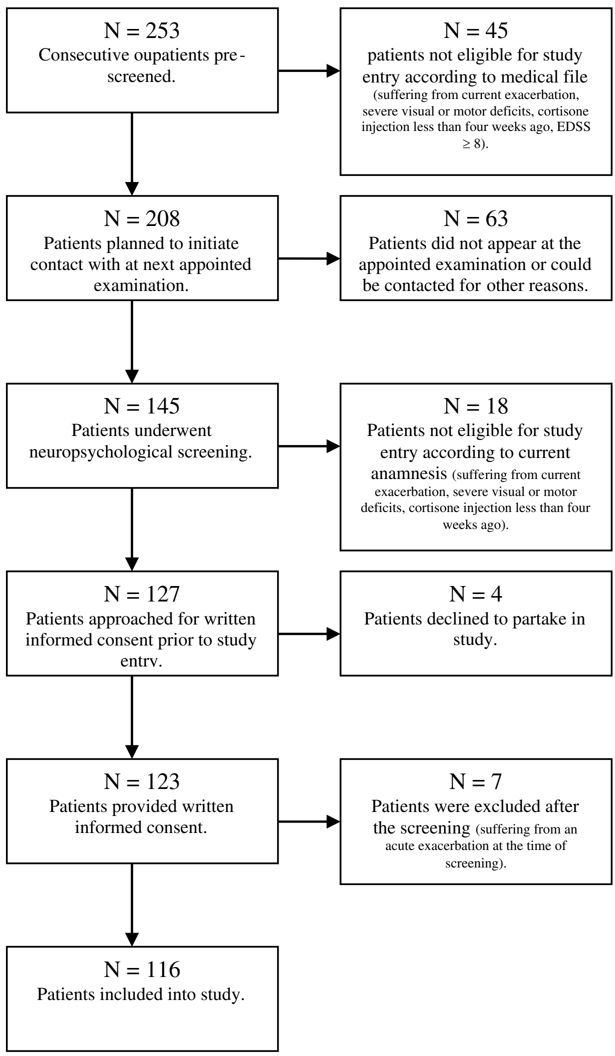
Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests*. New York, NY: Oxford University Press.

Tucha, L., Aschenbrenner, S., Koerts, J., & Lange, K. W. (2012). The Five-Point Test: Reliability, validity and normative data for children and adults. *PLoS ONE, 7*, e46080. doi:10.1371/journal.pone.0046080

Appendix 1. Calculation of parameters in the FPT

The calculation of FPT-scores is based on a procedure introduced by Goebel et al. (2009):
FPT-Productivity: Productivity is the number of all generated items. All repetitions, perseverated items or rule breakings are subtracted from this number. Connecting dots from different squares, drawing curled lines or lines not connecting dots are considered rule breakings.
FPT-Strategies: The strategy-score is calculated by summing up all items generated through the use of either rotating/mirroring the previous item (rotation strategy), or by adding an additional line to the previous item (addition strategy). This sum is then divided by the Productivity-score, indicating the number of items generated via strategy-use relative to the number of all generated items.
FPT-Repetitions: The number of perseverative designs is divided by the number of unique designs.

Appendix 2. Flow chart describing patient recruitment



Review

Neuropsychological Assessment in Multiple Sclerosis

An Overview

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Zertifizierte Fortbildung CME

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

Neuropsychologische Diagnostik bei Multipler Sklerose: eine Übersicht

Zusammenfassung: Neuropsychologische Defizite treten häufig bei Multipler Sklerose (MS) auf. In den vergangenen Jahrzehnten kam in diesem Zusammenhang eine große Zahl von diagnostischen Verfahren zum Einsatz. Obwohl möglicherweise bestimmte Aspekte der kognitiven Leistungsfähigkeit wie Informationsverarbeitungsgeschwindigkeit und Arbeitsgedächtnisleistung häufiger betroffen sind als andere Funktionen, gibt es doch im Zusammenhang mit MS kein spezifisches kognitives Defizitprofil. Dieser Artikel hat zum Ziel, einen Überblick über neuropsychologische Diagnoseverfahren bei MS zu geben. Des Weiteren wird dem Leser eine Entscheidung über die Anwendbarkeit spezifischer Prozeduren und die Beurteilung der Datenlage im Kontext der MS ermöglicht. Zuletzt werden Empfehlungen zur Zusammenstellung von Screeningverfahren und ausführlichen Testbatterien gegeben.

Schlüsselwörter: Multiple Sklerose, neuropsychologische Diagnose, kognitives 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-

https://doi.org/10.1024/1016-264X/a000197

Michaelis et al., 1991; Rao, Leo, Bernardin, & Unverzagt, 1991). Affected 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; Lazeron, Rombouts, 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 & Lautenbacher, 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 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, Burggraaff, 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 (Chiaravalloti & 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 made 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 o react 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 seen by far 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 one 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 seen 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 1. Procedures for assessing attentional functions.

Name	Source	Cognitive subfunction	Strengths and weaknesses
Symbol Digit Modalities Test (SDMT)	Smith (1982)	attention information processing speed	+ 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
Paced Auditory Serial Addition Test (PASAT)	Strauss et al. (2006)	divided attention working memory information processing speed	+ 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
Paced Visual Serial Addition Test (PVSAT)	Diamond et al. (1997)	visual information processing speed	+ visual alternative to the PASAT – minimal relevant study data
Digit-symbol coding (WAIS-IV)	Wechsler (2008)	psychomotor speed attention	+ alternative to the SDMT – minimal relevant study data – less suitable than the SDMT because of confounding with motor dysfunctions
Testbatterie zur Aufmerksamkeits-prüfung (TAP)	Zimmer-mann & Fimm (2009)	several aspects of intrinsic and selective attention	+ 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
Wiener Testsystem (Vienna System), i.e., ‘Determinationstest,’ ‘Reaktionstest’	Schuhfried (1992)	several aspects of intrinsic and selective attention	+/– strengths and weaknesses are analog to the TAP, though even less literature pertaining to MS exists for the Vienna System
Attention Network Test (ANT)	Fan et al. (2002)	several aspects of attention, including alertness, orien-ting, and executive control	+ assessment of several attentional processes in one subtest – very limited study data available
Faces Symbol Test (FST)	Scherer et al. (2007)	concentration and attention working memory	+ specifically designed for screening in MS – very limited study data available
Trail-Making Test (TMT)	Reitan (1955)	processing speed visuomotor tracking cognitive flexibility divided attention	+ extensive norms available + self-paced – motor dysfunctions are a confounding factor – influence of psychomotor speed on cognitive flexibility is unclear
d2	Bricken-kamp et al. (2010)	attention (both intensity and selectivity aspects)	+ extensive norms available – confounding with visuoperceptual processing – confounding with motor dysfunctions – little relevant study data in MS
Stroop Test (ST)	Bäumler (1985)	attention processing speed cognitive flexibility	+ some validation data exist in MS +/– contemporary studies see its usefulness more in the field of executive function – confounding with visuospatial deficits
Verbal and Nonver-bal Digit Span (WMS)	Härting (2000)	attention short term memory	+ some validation data exist in MS +/– most studies report that MS patients are unimpaired on these measures
brief test of attention (BTA)	Schretlen et al. (1996)	selective (divided) attention	+ supposedly indicative of cortico-cortical disconnections + some study data exist – little validation data available in an MS population

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 (Batista 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 Visual 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 (Staffen 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 Briken 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, Candliss, 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, Lupiànez, 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 (Scherer 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, & Tubridy 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; Cerasa 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., Härting 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. Peyser 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 (Sicotte 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 (Lafosse, 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.

The SRT is a multiple trial list learning test. Several scores can be derived, which supposedly represent specific component processes of verbal memory. Two of these scores are usually considered in the BRB screening procedure: Long-Term Storage (LTS) and Consistent Long-Term Retrieval (CLTR) (see Buschke & Fuld, 1974, or Strauss et al., 2006, for more information on these scores). Beatty et al. (1996) reported three different patterns of memory impairment in a study including 99 MS patients: The first group showed no impairments, whereas the second was rated as mildly to moderately impaired with superficially normal performance. Here, deficits cropped up only upon closer inspection of specific measures such as supra-span, inconsistent recall over learning trials, and deficient delayed recall. Finally, the third group was severely impaired with amnesia-like symptoms of encoding and retrieval deficits. Also, MS patients performed significantly worse than healthy controls on CLTR, but not on delayed recall (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). The authors concluded that the acquisition of verbal material is deficient in MS, whereas retention is largely

Table 2. Procedures for assessing memory function.

Name	Source	Cognitive subfunction	Strengths and weaknesses
Selective Reminding Test (SRT)	Buschke & Fuld (1974)	verbal memory (list learning, retention, recall)	+ vast amount of study data exist in MS + good differentiation between cognitively preserved and impaired patients
California Verbal Learning Test (CVLT)	Niemann et al. (2008)	verbal memory (list learning, retention, recall)	+ vast amount of study data exist in MS + good differentiation between cognitively preserved and impaired patients
Verbal Learning and Memory Test (VLMT)	Helmstaedter et al. (2001)	verbal memory (list learning, retention, recall)	+ roughly similar alternative to the CVLT + no compelling argument against employing it in MS – insufficient validation in MS
Logical Memory I & II (WMS)	Härting (2000)	verbal memory (story learning and story recall)	+ sufficient validation in MS + differentiates between patients and healthy controls +/– assesses an inherently different construct than list learning +/– patients tend to be less impaired on story recall than on list learning
Brief Visuospatial Memory Test – Revised (BVMT-R)	Benedict (1997)	nonverbal memory (learning and recall of abstract figures) visuospatial function	+ sufficient validation in MS + good differentiation between patients and healthy controls + six parallel forms +/– possible confounding with motor dysfunction is putatively controlled for by means of a copy trial
Spatial Recall Test (7/24 and 10/36)	Rao et al. (1984)	nonverbal memory (pattern learning and recall)	+ large amount of study data in MS + sufficient validation in MS – possible confounding factors with visuospatial ability, but also processing speed – inferior to the BVMT concerning predictive value
Rey-Osterrieth Complex Figure Test (ROCF)	Rey (1941), Osterrieth (1944)	nonverbal memory (figure learning and recall) visuospatial ability	+ allows insight into various cognitive abilities, including executive function – insufficient validation data in MS – differentiates less accurately than verbal memory tests between healthy controls and patients

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, Snook, 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, Helmstaedter, Lendt & Lux, 2001) as well as the logical memory subtests of the Wechsler Memory Scale (WMS, Härting 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 Helmstaedter, 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 (Härting et al., 2000). Several subtests of the WMS have been incorporated into test batteries for cognitive function in MS, among them 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, & Ruutiainen, 1997; Minden, Moes, Orav, Kaplan, & Reich, 1990; Olivares et al., 2005), and they differentiate between patients with deteriorated memory and preserved patients (Kujala, Portin, & Ruutiainen, 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). Beatty (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 Beatty (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 the 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 in clinical populations in general is the Rey-Osterrieth Complex Figure Test (ROCF, Rey, 1941; Osterrieth, 1944). The Rey-Figure is presented to the patient with the instruction to free-handedly copy it on a blank sheet of paper. (Also see the section on visuospatial abilities for further information.) The original figure and the copy are then removed and the patient is requested to draw the figure again from memory. The interval between copy and recall trial usually lies somewhere between 20 and 60 Minutes. Depending on the applied variant, an immediate recall trial can also be executed. Special care is required when choosing norms, as results differ depending on whether an immediate recall trial is included or not. The ROCF is part of the neuropsychological screening battery (NSB) by Franklin et al. (1988), which was proposed for use in MS. Even though the ROCF is still used as a clinical outcome parameter in contemporary studies (Chillemi et al., 2015; Fischer et al., 2014; Rocca et al., 2010), it has become less relevant in the neuropsychological assessment of MS patients, likely for several reasons: First, because of the complexity of the Rey-Figure, memorization heavily relies on successful perception and encoding. Thus, deficits in visuospatial abilities constitute a confounding factor in this test (Lezak, 2012). Though this aspect of the test provides the diagnostician with a wider range of information on possibly impaired cognitive functions, it can be considered disadvantageous in an MS population, where visuoperception may be impaired frequently (Rao et al., 1991; Schulz et al., 2006). Second, since this argument has been taken up by Benedict et al. (2002) in constituting the MACFIMS battery, the Rey-Figure and others were discarded in favor of the BVMT, resulting in a wider proliferation of the latter procedure. Finally, a meta-analysis by Zakzanis (2000) concluded that tests of verbal memory differentiated better between MS patients and healthy controls than the ROCF (though the opposite relation emerged for patients with chronic-progressive MS). This may be seen as an incentive to discard tests of nonverbal memory such as the ROCF in favor of a test of verbal memory in a screening.

Other Tests of Memory

A very small number of studies have investigated remote and autobiographical memory 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 Crovitz 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.

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

Table 3. Procedures for assessing executive functions.

Name	Source	Cognitive Subfunction	Strengths and Weaknesses
Wisconsin Card Sorting Test (WCST)	Heaton et al. (1993)	Concept formation and reasoning	+ 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)
Delis-Kaplan Executive Function Score (D-KEFS)	Delis et al. (2001)	Several aspects of executive function, assessed through nine subtests that may be employed separately	+ ideally suited for testing specific questions + some subtests include paradigms well researched in MS – insufficient validation of specific forms in MS
Standard Progressive Matrices (SPM)	Raven (1936)	Reasoning general cognitive ability	+ 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
Tower of Hanoi (ToH), Tower of London (ToL)	Goel & Grafman (1995), Tucha & Lange (2004)	planning and decision-making logical problem solving	+ 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
Regensburger Wortflüssigkeitstest (RWT); Controlled Oral Word Association Test (COWAT); Word List Generation (WLG)	Aschenbrenner et al. (2000); Benton & Hamsher (1989); Rao et al. (1990)	verbal fluency language ability psychomotor speed semantic memory	+ 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
Five Point Test (FPT)	Regard et al. (1982)	nonverbal fluency psychomotor speed	+ short and easy to administer + norms for strategy use allow qualitative assessment – only limited study data available – confounding with motor disability
TAP subtests Flexibility, Go/NoGo, Shift of Attention, Working Memory	Zimmermann & Fimm (2009)	several aspects of attentional processes and executive control	+ 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
Stroop-Test	Bäumler (1985)	attention processing speed cognitive flexibility inhibition	+ 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
Trail-Making Test (TMT)	Reitan (1955)	processing speed visuomotor tracking cognitive flexibility divided attention	– confounding with motor and visuospatial dysfunction as well as processing speed – does not discriminate well between patients and controls

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

Name	Source	Cognitive Subfunction	Strengths and Weaknesses
Paced Auditory Serial Addition Test (PASAT)	Strauss et al. (2006)	working memory divided attention processing speed	+ differentiates well between cognitively impaired and preserved patients + short + 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
Testbatterie zur Aufmerksamkeitsprüfung (TAP), subtest Working Memory	Zimmermann & Fimm (2009)	working memory attention	+ sufficient norms – confounding factors are attention and psychomotor speed – only limited study data in MS
Verbal and Nonverbal Digit Span (WMS) backwards	Härting (2000)	working memory attention short-term memory	+ some validation data exist in MS + very basic and easily executed test – attention is a confounding factor – appears to differentiate only marginally between patients and controls
Wechsler Adult Intelligence Scale (WAIS)	Wechsler (2008)	working memory attention short-term memory	+/– pros/cons basically comparable to Verbal Digit Span backwards, but less clinical data in MS

patients have to adapt to the new situation. This paradigm can be considered a measure of executive function since it requires higher-order reasoning abilities, strategic planning, and the ability to adapt to changing environmental contingencies (Heaton et al., 1993). It was first employed by Rao, Hammeke, and Speech (1987) in a study comparing relapsing-remitting MS (RRMS), chronic-progressive MS (CPMS), and chronic-pain patients with a healthy control group. They reported that RRMS patients did not score worse than controls on any of the WCST parameters, but that CPMS patients achieved significantly fewer categories and made more perseverations. Two additional studies comparing MS patients with healthy controls concerning their performance on several cognitive parameters – among them the WCST essentially produced comparable results (Rao et al., 1989b; Rao et al., 1991). Consequently, the WCST was recommended as part of a neuropsychological test battery in MS (Peyser et al., 1990). A comparison with magnetic resonance imaging resulted in the conclusion that those patients with lesion load predominantly in frontal white-matter areas scored worse on the WCST than those with lesions predominantly elsewhere or with an overall minimal lesion load (Arnett et al., 1994). Beatty, Hames, Blanco, Paul, and Wilbanks (1995a) compared the results of several measures of verbal and nonverbal reasoning tasks in a MS population and in a healthy control group. Since MS patients achieved fewer categories on all applied measures, they concluded that patients' difficulties 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. For the most part, these tests are modified versions of previously existing executive 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 CCST, 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 (Delis 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 (Brissart 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., Tower of Hanoi (i.e., Goel & Grafman, 1995) and Tower of London (i.e., Tucha & Lange, 2004) – are most frequently represented. Patients move a number of disks or beads from a starting position to a predefined goal position by employing 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 & Mathes-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 Wortflüssigkeitstest (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 (Bodden & 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., Bäumler & 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, Portin, Revensuo, 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 (Lamargue-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, Tulsky, Lengenfelder, and Chiaravalloti (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 (PASAT) 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 (PASAT) 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 an 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 certainly atypical for MS. Furthermore, MRIs of all patients included in this study showed a high lesion load with confluent 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 fulfil 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 reported to cover these domains (Zimmermann & Fimm, 2009). It has also seen some use in MS-related studies (Fischer et al., 2014; Hansen et al., 2015; Penner et al., 2001; Schulz et al., 2006). Additional testing in this domain might include tests of digit span or psychomotor speed.

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 not 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-

Table 4. Minimal Assessment of Cognitive Function in MS (MACFIMS)-Protocol according to Benedict et al. (2002).

Processing speed/Working memory:
– Paced Auditory Serial Addition Test
– Symbol Digit Modalities Test
Learning and Memory
– California Verbal Learning Test-II
– Brief Visuospatial Memory Test – R
Executive functions
– D-KEFS Sorting Test
Visual perception/Spatial processing
– Judgment of Line Orientation Test
Language/other
– Controlled Oral Word Association Test

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 Erschöpfungsinventar für Multiple Sclerosis (WEIMUS, fatigue inventory for Multiple Sclerosis Würzburg Flachenecker, 2008) and the Fatigue Scale for Motor and Cognitive Functions (FSMC, 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.

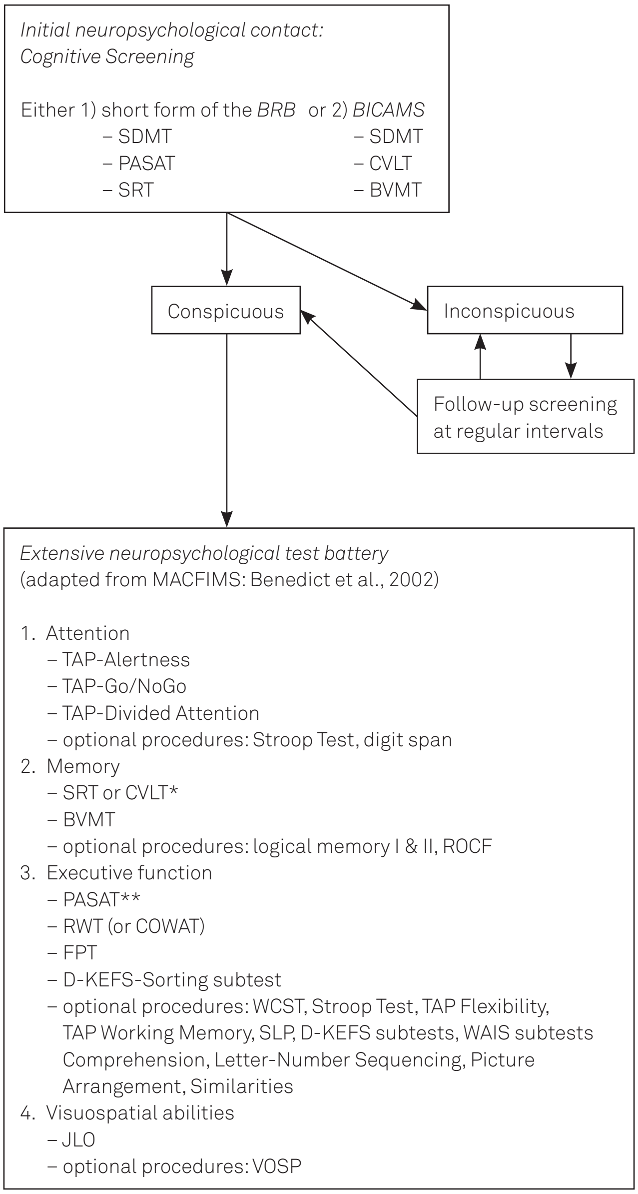

Figure 1. Proposed adapted rationale for neuropsychological assessment. *either SRT or CVLT, whichever did not occur in the screening, **only if PASAT was not already executed during the screening.

References

Achiron, A., & Barak, Y. (2003). Cognitive impairment in probable multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*, 443–446.

Amato, M.P., Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *Journal of the Neurological Sciences*, *245*(1), 41–46.

Amato, M.P., Goretti, B., Viterbo, R.G., Portaccio, E., Niccolai, C., Hakiki, B., ... Trojano, M. (2014). Computer-assisted rehabilitation of attention in patients with multiple sclerosis: Results of a randomized, double-blind trial. *Multiple Sclerosis Journal*, *20*(1), 91–98.

Amato, N., Cursi, M., Rodegher, M., Moiola, L., Colombo, B., Falautano, M., ... Leocani, L. (2016). Stroop event-related potentials as a bioelectrical correlate of frontal lobe dysfunction in multiple sclerosis. *Multiple Sclerosis and Demyelinating Disorders*, *1*(1), 8–17.

Andrade, V.M., Bueno, O.F., Oliveira, M.G. M., Oliveira, A.S., Oliveira, E.M., & Miranda, M.C. (1999). Cognitive profile of patients with relapsing remitting multiple sclerosis. *Arquivos de Neuropsiquiatria*, *57*(3B), 775–783.

Anzola, G.P., Bevilacqua, L., Cappa, S.F., Capra, R., Faglia, L., Farina, E., ... Vignolo, L.A. (1990). Neuropsychological assessment in patients with relapsing-remitting multiple sclerosis and mild functional impairment: Correlation with magnetic resonance imaging. *Journal of Neurology, Neurosurgery & Psychiatry*, *53*, 142–145.

Archibald, C.J., & Fisk, J.D. (2000). Information processing efficiency in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *22*, 686–701.

Arnett, P.A., Rao, S.M., Bernardin, L., Grafman, J., Yetkin, F.Z., & Lobeck, L. (1994). Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. *Neurology*, *44*(3 Part 1), 420–420.

Arnett, P.A., Rao, S.M., Grafman, J., Bernardin, L., Luchetta, T., Binder, J.R., & Lobeck, L. (1997). Executive functions in multiple sclerosis: An analysis of temporal ordering, semantic encoding, and planning abilities. *Neuropsychology*, *11*, 535–544.

Arnett, P.A., Higginson, C.I., & Randolph, J.J. (2001). Depression in multiple sclerosis: Relationship to planning ability. *Journal of the International Neuropsychological Society*, *7*, 665–674.

Arnett, P.A. (2005). Longitudinal consistency of the relationship between depression symptoms and cognitive functioning in multiple sclerosis. *CNS Spectrums*, *10*, 372–382.

Arnett, P.A., Barwick, F.H., & Beeney, J.E. (2008). Depression in multiple sclerosis: Review and theoretical proposal. *Journal of the International Neuropsychological Society*, *14*, 691–724.

Aschenbrenner, S., Tucha, O., & Lange, K.W. (2000). *Regensburger Wortflüssigkeits-Test: RWT/Regensburg word fluency test*. Göttingen: Hogrefe.

Baddeley, A. (2000). The episodic buffer: A new component of working memory? *Trends in Cognitive Sciences*, *4*, 417–423.

Batista, S., Zivadinov, R., Hoogs, M., Bergsland, N., Heininen-Brown, M., Dwyer, M.G., ... Benedict, R.H. (2012). Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. *Journal of Neurology*, *259*(1), 139–146.

Bäumler, G., & Stroop, J.R. (1985). *Farbe-Wort-Interferenztest nach JR Stroop (FWIT), colour-word interference test*. Göttingen: Hogrefe.

Beatty, W.W., Goodkin, D.E., Monson, N., Beatty, P.A., & Hertsgaard, D. (1988). Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. *Archives of Neurology*, *45*, 611–619.

Beatty, W.W., Goodkin, D.E., Monson, N., & Beatty, P.A. (1989). Cognitive disturbances in patients with relapsing remitting multiple sclerosis. *Archives of Neurology*, *46*, 1113–1119.

Beatty, W.W. (1993). Age differences on the California Card Sorting Test: Implications for the assessment of problem solving by the elderly. *Bulletin of the Psychonomic Society*, *31*, 511–514.

Beatty, W.W., & Monson, N. (1994). Picture and motor sequencing in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *16*, 165–172.

Beatty, W.W., Hames, K.A., Blanco, C.R., Paul, R.H., & Wilbanks, S.L. (1995a). Verbal abstraction deficit in multiple sclerosis. *Neuropsychology*, *9*, 198–205.

Beatty, W.W., Paul, R.H., Blanco, C.R., Hames, K.A., & Wilbanks, S.L. (1995b). Attention in multiple sclerosis: Correlates of impairment on the WAIS-R Digit Span Test. *Applied Neuropsychology*, *2*, 139–144.

Beatty, W.W., Paul, R.H., Wilbanks, S.L., Hames, K.A., Blanco, C.R., & Goodkin, D.E. (1995c). Identifying multiple sclerosis patients with mild or global cognitive impairment using the Screening Examination for Cognitive Impairment (SEFCI). *Neurology*, *45*, 718–723.

Beatty, W.W., & Monson, N. (1996). Problem solving by patients with multiple sclerosis Comparison of performance on the Wisconsin and California Card Sorting Tests. *Journal of the International Neuropsychological Society*, *2*, 134–140.

Beatty, W.W., Wilbanks, S.L., Blanco, C.R., Hames, K.A., Tivis, R., & Paul, R.H. (1996). Memory disturbance in multiple sclerosis: Reconsideration of patterns of performance on the selective reminding test. *Journal of Clinical and Experimental Neuropsychology*, *18*(1), 56–62.

Beatty, W.W. (2002). Fluency in multiple sclerosis: Which measure is best? *Multiple Sclerosis Journal*, *8*, 261–264.

Beatty, W.W., & Aupperle, R.L. (2002). Sex differences in cognitive impairment in multiple sclerosis. *The Clinical Neuropsychologist*, *16*, 472–480.

Beatty, W.W. (2004). RBANS analysis of verbal memory in multiple sclerosis. *Archives of Clinical Neuropsychology*, *19*, 825–834.

Beblo, T., & Lautenbacher, S. (2006). *Neuropsychologie der Depression. Band 6 in Fortschritte der Neuropsychologie (neuropsychology of depression. Volume 6 of Advances in Neuropsychology)*. Göttingen: Hogrefe.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). Beck depression inventory-II. *San Antonio*, *78*, 490–498.

Benedict, R.H. B. (1997). *Brief visuospatial memory test-revised: Professional manual*. Odessa, FL: Psychological Assessment Resources.

Benedict, R.H., Priore, R.L., Miller, C., Munschauer, F., & Jacobs, L. (2001). Personality disorder in multiple sclerosis correlates with cognitive impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(1), 70–76.

Benedict, R.H., Fischer, J.S., Archibald, C.J., Arnett, P.A., Beatty, W.W., Bobholz, J., ... Munschauer, F. (2002). Minimal neuropsychological assessment of MS patients: A consensus approach. *The Clinical Neuropsychologist*, *16*, 381–397.

Benedict, R.H., Munschauer, F., Linn, R., Miller, C., Murphy, E., Foley, F., & Jacobs, L. (2003). Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Multiple Sclerosis Journal*, *9*(1), 95–101.

Benedict, R.H. (2005). Effects of using same- versus alternate-form memory tests during short-interval repeated assessments in multiple sclerosis. *Journal of the International Neuropsychological Society*, *11*, 727–736.

Benedict, R.H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*, 549–558.

Benedict, R.H., Amato, M.P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., ... Penner, I. (2012). Brief International Cognitive Assessment for MS (BICAMS): International standards for validation. *BMC Neurology*, *12*(1), 55–62.

Benedict, R.H., DeLuca, J., Phillips, G., LaRocca, N., Hudson, L.D., & Rudick, R. (2017). Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Multiple Sclerosis Journal*, *23*, 721–733.

Benton, A.L., Hamsher, K. d, & Sivan, A. (1989). Multilingual aphasia examination. Iowa City, IA: AJA Associates.

Benton, A.L. (1994). *Contributions to neuropsychological assessment: A clinical manual*. New York: Oxford University Press.

Bobholz, J.A., & Rao, S.M. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Current Opinion in Neurology*, *16*, 283–288.

Bodden, M., & Kalbe, E. (2010). Neuropsychological diagnostic in cognitive deficits. *Nervenheilkunde*, *29*, 761–768.

Bonavita, S., Sacco, R., Della Corte, M., Esposito, S., Sparaco, M., d'Ambrosio, A., ... Corbo, D. (2015). Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: An exploratory study. *Journal of Neurology*, *262*(1), 91–100.

Brickenkamp, R., Schmidt-Atzert, L., & Liepmann, D. (2010). *Test d2-Revision: Aufmerksamkeits-und Konzentrationstest (attentiveness endurance test)*. Göttingen: Hogrefe.

Briken, S., Gold, S.M., Patra, S., Vettorazzi, E., Harbs, D., Tallner, A., ... Heesen, C. (2014). Effects of exercise on fitness and cognition in progressive MS: A randomized, controlled pilot trial. *Multiple Sclerosis Journal*, *20*, 382–390.

Brissart, H., Morele, E., Baumann, C., Perf, M.L., Leininger, M., Taillemite, L., ... Debouverie, M. (2013). Cognitive impairment among different clinical courses of multiple sclerosis. *Neurological Research*, *35*, 867–872.

Brittain, J.L., La Marche, J.A., Reeder, K.P., Roth, D.L., & Boll, T.J. (1991). Effects of age and IQ on paced auditory serial addition task (PASAT) performance. *The Clinical Neuropsychologist*, *5*, 163–175.

Burschka, J.M., Keune, P.M., Menge, U., Hofstadt-van Oy, U., Oschmann, P., & Hoos, O. (2012). An exploration of impaired walking dynamics and fatigue in multiple sclerosis. *BMC Neurology*, *12*(1), 161.

Buschke, H., & Fuld, P.A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*, *24*, 1019–1019.

Cader, S., Cifelli, A., Abu-Omar, Y., Palace, J., & Matthews, P.M. (2006). Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. *Brain*, *129*, 527–537.

Caine, E.D., Bamford, K.A., Schiffer, R.B., Shoulson, I., & Levy, S. (1986). A controlled neuropsychological comparison of Huntington's disease and multiple sclerosis. *Archives of Neurology*, *43*, 249–254.

Calabrese, M., Filippi, M., & Gallo, P. (2010). Cortical lesions in multiple sclerosis. *Nature Reviews Neurology*, *6*, 438–444.

Calabrese, P. (2003). Kognitive Störungen bei Multipler Sklerose (cognitive dysfunction in multiple sclerosis). *Psychoneuro*, *29*, 344–348.

Calabrese, P. (2006). Neuropsychology of multiple sclerosis. *Journal of Neurology*, *253*, i10–i15.

Callejas, A., Lupiàñez, J., Funes, M.J., & Tudela, P. (2005). Modulations among the alerting, orienting, and executive control networks. *Experimental Brain Research*, *167*(1), 27–37.

Camp, S.J., Stevenson, V.L., Thompson, A.J., Miller, D.h., Borras, C., Auriacombe, S., ... Herisse-Dulo, L. (1999). Cognitive function in primary progressive and transitional progressive multiple sclerosis. *Brain*, *122*, 1341–1348.

Camp, S.J., Stevenson, V.L., Thompson, A.J., Ingle, G.T., Miller, D.h., Borras, C., ... Filippi, M. (2005). A longitudinal study of cognition in primary progressive multiple sclerosis. *Brain*, *128*, 2891–2898.

Cerasa, A., Gioia, M.C., Valentino, P., Nisticò, R., Chiriaco, C., Pirritano, D., ... Talarico, T. (2013). Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: A randomized trial with fMRI correlates. *Neurorehabilitation and Neural Repair*, *27*, 284–295.

Chiaravalloti, N.D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*, 1139–1151.

Chiaravalloti, N.D., Balzano, J., Moore, N.B., & DeLuca, J. (2009). The Open-Trial Selective Reminding Test (OT-SRT) as a tool for the assessment of learning and memory. *The Clinical Neuropsychologist*, *23*, 231–254.

Chillemi, G., Scalera, C., Terranova, C., Calamuneri, A., Buccafusca, M., Dattola, V., ... Quartarone, A. (2015). Cognitive processes and cognitive reserve in multiple sclerosis. *Archives italiennes de biologie*, *153*(1), 19–24.

Christodoulou, C., Krupp, L.B., Liang, Z., Huang, W., Melville, P., Roque, C., ... Li, L. (2003). Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. *Neurology*, *60*, 1793–1798.

Clemmons, D.C., Fraser, R.T., Rosenbaum, G., Getter, A., & Johnson, E. (2004). An abbreviated neuropsychological battery in multiple sclerosis vocational rehabilitation: Findings and implications. *Rehabilitation Psychology*, *49*, 100–105.

Comi, G., Rovaris, M., Leocani, L., Martinelli, V., & Filippi, M. (2000). Assessment of the damage of the cerebral hemispheres in MS using neuroimaging techniques. *Journal of the Neurological Sciences*, *172*, S63–S66.

Cooley, E.L., & Morris, R.D. (1990). Attention in children: A neuropsychologically based model for assessment. *Developmental Neuropsychology, 6,* 239–274.

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*, 323–338.

De Sonneville, L.M.J., Boringa, J.B., Reuling, I.E.W., Lazeron, R.H. C., Ader, H.J., & Polman, C.H. (2002). Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia*, *40*, 1751–1765.

Delis, D.C., Bihrle, A., Janowsky, J.S., Squire, L.R., & Shimamura, A.P. (1989). Fractionation of problem-solving deficits in frontal-lobe patients. *Journal of Clinical & Experimental Neuropsychology*, *11*, 50–58.

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). *Delis-Kaplan executive function system (D-KEFS)*. San Antonio, TX: Psychological Corporation.

DeLuca, J., Gaudino, E.A., Diamond, B.J., Christodoulou, C., & Engel, R.A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *20*, 376–390.

DeLuca, J., Chelune, G.J., Tulsky, J., Lengenfelder, J., Chiaravalloti, N.D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology, 26*, 550–562.

Demaree, H.A., DeLuca, J., Gaudino, E.A., & Diamond, B.J. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *Journal of Neurology, Neurosurgery & Psychiatry*, *67*, 661–663.

Denney, D.R., Sworowski, L.A., & Lynch, S.G. (2005). Cognitive impairment in three subtypes of multiple sclerosis. *Archives of Clinical Neuropsychology*, *20*, 967–981.

Denney, D.R., & Lynch, S.G. (2009). The impact of multiple sclerosis on patients' performance on the Stroop Test: Processing speed versus interference. *Journal of the International Neuropsychological Society*, *15*, 451–458.

DeSousa, E.A., Albert, R.H., & Kalman, B. (2002). Cognitive impairments in multiple sclerosis: A review. *American Journal of Alzheimer's Disease and Other Dementias*, *17*, 23–29.

D'esposito, M., Onishi, K., Thompson, H., Robinson, K., Armstrong, C., & Grossman, M. (1996). Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology*, *10*(1), 51–56.

Diamond, B.J., Deluca, J., Kim, H., & Kelley, S.M. (1997). The question of disproportionate impairments in visual and auditory information processing in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *19*(1), 34–42.

Drew, M., Tippett, L.J., Starkey, N.J., & Isler, R.B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: A descriptive study. *Archives of Clinical Neuropsychology*, *23*(1), 1–19.

Duong, M.A., Boulanouar, K., Audoin, B., Treseras, S., Ibarrola, D., Malikova, I., ... Cozzone, P.J. (2005). Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. *Neuroimage*, *24*, 533–538.

Engel, C., Greim, B., & Zettl, U.K. (2005). Kognitive Defizite bei Multipler Sklerose (Cognitive dysfunctions in multiple sclerosis patients). *Der Nervenarzt*, *76*, 943–953.

Ernst, A., Blanc, F., Voltzenlogel, V., De Seze, J., Chauvin, B., & Manning, L. (2013). Autobiographical memory in multiple sclerosis patients: Assessment and cognitive facilitation. *Neuropsychological Rehabilitation*, *23*, 161–181.

Faiss, J.H., Dähne, D., Baum, K., Deppe, R., Hoffmann, F., Köhler, W., ... Penner, I.K. (2014). Reduced magnetisation transfer ratio in cognitively impaired patients at the very early stage of multiple sclerosis: A prospective, multicenter, cross-sectional study. *BMJ Open*, *4*(4), e004409.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., & Posner, M.I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*, 340–347.

Filley, C.M., Heaton, R.K., Thompson, L., & Nelson, L.M. (1990). Effects of disease course on neuropsychological functioning. In Rao (Ed.), *Neurobehavioral Aspects of Multiple Sclerosis*, New York: Oxford University Press.

Fischer, J.S. (1988). Using the Wechsler Memory Scale-Revised to detect and characterize memory deficits in multiple sclerosis. *The Clinical Neuropsychologist*, *2*, 149–172.

Fischer, J.S., Rudick, R.A., Cutter, G.R., & Reingold, S.C. (1999). The Multiple Sclerosis Functional Composite measure (MSFC): An integrated approach to MS clinical outcome assessment. *Multiple Sclerosis Journal*, *5*, 244–250.

Fischer, J.S. (2001). Cognitive impairment in multiple sclerosis. *Neurological Disease and Therapy*, *53*, 233–256.

Fischer, M., Kunkel, A., Bublak, P., Faiss, J.H., Hoffmann, F., Sailer, M., ... Köhler, W. (2014). How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? *Journal of the Neurological Sciences*, *343*(1), 91–99.

Fisk, J.D., & Archibald, C.J. (2001). Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis. *Journal of the International Neuropsychological Society*, *7*, 363–372.

Flachenecker, P. (2008). Validierung des Würzburger Erschöpfungsinventars bei Multipler Sklerose (WEIMuS), Würzburg fatigue inventory for multiple sclerosis. *Neurologie & Rehabilitation*, *14,* 299–306.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C.A., Kartsounis, L.D., Thompson, A.J., ... Ron, M.A. (1997). Executive function in multiple sclerosis: The role of frontal lobe pathology. *Brain*, *120*(1), 15–26.

Forn, C., Belenguer, A., Parcet-Ibars, M.A., & Avila, C. (2008). Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). *Journal of Clinical and Experimental Neuropsychology*, *30*, 789–796.

Franklin, G.M., Heaton, R.K., Nelson, L.M., Filley, C.M., & Seibert, C. (1988). Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis. *Neurology*, *38*, 1826–1826.

Gaines, J.J., Gavett, R.A., Lynch, J.J., Bakshi, R., & Benedict, R.H. (2008). New error type and recall consistency indices for the Brief Visuospatial Memory Test–Revised: Performance in healthy adults and multiple sclerosis patients. *The Clinical Neuropsychologist*, *22*, 851–863.

Galanter, E., & Pribram, K.H. (1960). *Plans and the structure of behavior*. New York: Holt, Rinehart and Winston.

Genova, H.M., Lengenfelder, J., Chiaravalloti, N.D., Moore, N.B., & DeLuca, J. (2012). Processing speed versus working memory: Contributions to an information-processing task in multiple sclerosis. *Applied Neuropsychology: Adult*, *19*, 132–140.

Glanz, B.I., Holland, C.M., Gauthier, S.A., Amunwa, E.L., Liptak, Z., Houtchens, M.K., ... Weiner, H.L. (2007). Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. *Multiple Sclerosis Journal*, *13*, 1004–1010.

Goel, V., & Grafman, J. (1995). Are the frontal lobes implicated in "planning" functions? Interpreting data from the Tower of Hanoi. *Neuropsychologia*, *33*, 623–642.

Gontkovsky, S.T., Vickery, C.D., & Beatty, W.W. (2004). Construct validity of the 7/24 spatial recall test. *Applied Neuropsychology*, *11*, 75–84.

Goodkin, D.E., Hertsgaard, D., & Seminary, J. (1988). Upper extremity function in multiple sclerosis: Improving assessment sensitivity with box-and-block and nine-hole peg tests. *Archives of Physical Medicine and Rehabilitation*, *69*, 850–854.

Grabner, R.H., Popotnig, F., Ropele, S., Neuper, C., Gorani, F., Petrovic, K., ... Enzinger, C. (2008). Brain activation patterns elicited by the Faces Symbol Test – A pilot fMRI study. *Multiple Sclerosis*, *14*, 354–363.

Graham, K.S., & Hodges, J.R. (1997). Differentiating the roles of the hippocampus complex and the neocortex in long-term memory storage: Evidence from the study of semantic dementia and Alzheimer's disease. *Neuropsychology*, *11*(1), 77.

Greene, Y.M., Tariot, P.N., Wishart, H., Cox, C., Holt, C.J., Schwid, S., & Noviasky, J. (2000). A 12-week, open trial of donepezil hydrochloride in patients with multiple sclerosis and associated cognitive impairments. *Journal of Clinical Psychopharmacology*, *20*, 350–356.

Greim, B., & Zettl, U.K. (2009). Neuropsychologische Störungen bei Multipler Sklerose (Neuropsychological disorders in multiple sclerosis). *Fortschritte der Neurologie· Psychiatrie*, *77*(S01), S28–S31.

Grigsby, J., Kaye, K., & Busenbark, D. (1994). Alphanumeric sequencing: A report on a brief measure of information processing used among persons with multiple sclerosis. *Perceptual and Motor Skills, 78*, 883–887.

Gronwall, D.M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*, 367–373.

Hansen, S., Muenssinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P., & Keune, P.M. (2015). Cognitive screening tools in multiple sclerosis revisited: Sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. *BMC Neurology*, *15*(1), 246–252.

Hansen, S., Muenssinger, J., Kronhofmann, S., Lautenbacher, S., Oschmann, P., & Keune, P.M. (2017). Cognitive screening in Multiple Sclerosis: The Five-Point Test as a substitute for the PASAT in measuring executive function. *The Clinical Neuropsychologist*, *31*(1), 179–192.

Härting, C., Markowitsch, H.J., Neufeld, H., Calabrese, P., Deisinger, K., & Kessler, J. (2000). *Die Wechsler Memory Scale-revised. Deutschsprachige Adaptation (Wechsler Memory Scale-revised edition)*. Bern: Huber.

Hautzinger, M., Bailer, M., Hofmeister, D., & Keller, F. (2012). Allgemeine depressionsskala (ADS) (center for epidemiological-depression scale [CES-D]). *Psychiatrische Praxis*, *39*, 302–304.

Heaton, R.K., Nelson, L.M., Thompson, D.S., Burks, J.S., & Franklin, G.M. (1985). Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of Consulting and Clinical Psychology*, *53*, 103.

Heaton, R.K., Chelune, G.J., Curtiss, G., Kay, G.G., & Talley, J.L. (1993). *Wisconsin card sorting test*. Odessa, FL. Psychological Assessment Resources.

Heesen, C., Schulz, K.H., Fiehler, J., Von der Mark, U., Otte, C., Jung, R., … Gold, S.M. (2010). Correlates of cognitive dysfunction in multiple sclerosis. *Brain, Behavior, and Immunity*, *24*, 1148–1155.

Helmstaedter, C., Lendt, M., Lux, S. (2001). *VLMT: Verbaler Lern- und Merkfähigkeitstest (AVLT: Auditory verbal learning test)* Göttingen: Beltz Test.

Helmstaedter, C., Wietzke, J., & Lutz, M.T. (2009). Unique and shared validity of the "Wechsler Logical Memory Test," the "California Verbal Learning Test," and the "Verbal Learning and Memory Test" in patients with epilepsy. *Epilepsy Research*, *87*, 203–212.

Henry, J.D., & Crawford, J.R. (2005). A meta-analytic review of verbal fluency deficits in depression. *Journal of Clinical and Experimental Neuropsychology*, *27*(1), 78–101.

Henry, J.D., & Beatty, W.W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia, 44*, 1166–1174.

Hildebrandt, H., Brokate, B., Lanz, M., Ternes, T., & Timm, C. (2003). Exekutivfunktionsleistungen bei Patienten mit multipler Sklerose (Executive functions in patients with multiple sclerosis). *Aktuelle Neurologie*, *30*, 118–126.

Hoffmann, S., Tittgemeyer, M., & von Cramon, D.Y. (2007). Cognitive impairment in multiple sclerosis. *Current Opinion in Neurology*, *20*, 275–280.

Hooper, E.H. (1983). *Hooper visual organization test (VOT)*. Torrance, CA: Western Psychological Services

Huijbregts, S.C.J., Kalkers, N.F., De Sonneville, L.M.J., De Groot, V., Reuling, I.E.W., & Polman, C.H. (2004). Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology*, *63*, 335–339.

Hulst, H.E., Gehring, K., Uitdehaag, B.M., Visser, L.H., Polman, C.H., Barkhof, F., … Geurts, J.J. (2014). Indicators for cognitive performance and subjective cognitive complaints in multiple sclerosis: A role for advanced MRI? *Multiple Sclerosis Journal*, *20*, 1131–1134.

Ishigami, Y., Fisk, J.D., Wojtowicz, M., & Klein, R.M. (2013). Repeated measurement of the attention components of patients with multiple sclerosis using the Attention Network Test-Interaction (ANT-I): Stability, isolability, robustness, and reliability. *Journal of Neuroscience Methods*, *216*(1), 1–9.

Ivnik, R.J. (1978). Neuropsychological stability in multiple sclerosis. *Journal of Consulting and Clinical Psychology*, *46*, 913–923.

Jasse, L., Vukusic, S., Durand-Dubief, F., Vartin, C., Piras, C., Bernard, M., … Tilikete, C. (2013). Persistent visual impairment in multiple sclerosis: Prevalence, mechanisms, and resulting disability. *Multiple Sclerosis Journal*, *19*, 1618–1626.

Joffe, R.T., Lippert, G.P., Gray, T.A., Sawa, G., & Horvath, Z. (1987). Mood disorder and multiple sclerosis. *Archives of Neurology*, *44*, 376–378.

Johnson, S.K., Lange, G., DeLuca, J., Korn, L.R., & Natelson, B. (1997). The effects of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis, and depression. *Applied Neuropsychology*, *4*, 145–153.

Kail, R. (1998). Speed of information processing in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *20*(1), 98–106.

Kaur, P., & Bennett, J.L. (2007). Optic neuritis and the neuro-ophthalmology of multiple sclerosis. *International Review of Neurobiology*, *79*, 633–663.

Keune, P.M., Hansen, S., Weber, E., Zapf, F., Habich, J., Wolf, S., Schönenberg, M., Oschmann, P. (submitted). *Exploring neurophysiologic monitoring parameters and cognitive functioning in multiple sclerosis (MS): The EEG theta/beta ratio and attention performance.*

Kessels, R.P., Van Zandvoort, M.J., Postma, A., Kappelle, L.J., & De Haan, E.H. (2000). The Corsi block-tapping task: Standardization and normative data. *Applied Neuropsychology*, *7*, 252–258.

Kolber, P., Montag, S., Fleischer, V., Luessi, F., Wilting, J., Gawehn, J., … Zipp, F. (2015). Identification of cortical lesions using DIR and FLAIR in early stages of multiple sclerosis. *Journal of Neurology*, *262*, 1473–1482.

Kopelman, M.D., Wilson, B.A., & Baddeley, A.D. (1989). The autobiographical memory interview: A new assessment of autobiographical and personal semantic memory in amnesic patients. *Journal of Clinical and Experimental Neuropsychology*, *11*, 724–744.

Kourtidou, P., Kasselimis, D., Potagas, C., Zalonis, I., & Evdokimidis, I. (2015). Effects of mental flexibility and motor dysfunction on cognitive performance in patients with parkinson's disease. *Archives of Neuroscience*, *2*(3). URL: http://archneurosci.com/21087.fulltext.

Krupp, L.B., & Elkins, L.E. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology*, *55*, 934–939.

Kujala, P., Portin, R., Revonsuo, A., & Ruutiainen, J. (1994). Automatic and controlled information processing in multiple sclerosis. *Brain*, *117*, 1115–1126.

Kujala, P., Portin, R., Revonsuo, A., & Ruutiainen, J. (1995). Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *59*(1), 77–82.

Kujala, P., Portin, R., & Ruutiainen, J. (1997). The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. *Brain*, *120*, 289–297.

Kunkel, A., Fischer, M., Faiss, J., Dähne, D., Köhler, W., & Faiss, J.H. (2015). Impact of natalizumab treatment on fatigue, mood, and aspects of cognition in relapsing–remitting multiple sclerosis. *Frontiers in Neurology*, *6*. URL:10.3389/fneur.2015.00097.

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). *Neurology*, *33*, 1444–1444.

Küst, J., & Dettmers, C. (2014). Fahreignung bei Multipler Sklerose (Driving ability with multiple sclerosis). *Der Nervenarzt*, *85*, 829–834.

Lafosse, J.M., Mitchell, S.M., Corboy, J.R., & Filley, C.M. (2013). The nature of verbal memory impairment in multiple sclerosis: A list-learning and meta-analytic study. *Journal of the International Neuropsychological Society*, *19*, 995–1008.

Lamargue-Hamel, D., Deloire, M., Saubusse, A., Ruet, A., Taillard, J., Philip, P., & Brochet, B. (2015). Cognitive evaluation by tasks in a virtual reality environment in multiple sclerosis. *Journal of the Neurological Sciences*, *359*, 94–99.

Langdon, D. (2010). Cognitive impairment in multiple sclerosis – Recent advances and future prospects. *European Neurological Review, 5*(1), 69–72.

Langdon, D.W., Amato, M.P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., … Penner, I.K. (2012). Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Multiple Sclerosis Journal*, *18*, 891–898.

Lazeron, R.H., Rombouts, S.A., Scheltens, P., Polman, C.H., & Barkhof, F. (2004). An fMRI study of planning-related brain activity in patients with moderately advanced multiple sclerosis. *Multiple Sclerosis Journal*, *10*, 549–555.

Leavitt, V.M., Wylie, G., Genova, H.M., Chiaravalloti, N.D., & DeLuca, J. (2012). Altered effective connectivity during performance of an information processing speed task in multiple sclerosis. *Multiple Sclerosis Journal*, *18*, 409–417.

Lengenfelder, J., Bryant, D., Diamond, B.J., Kalmar, J.H., Moore, N.B., & DeLuca, J. (2006). Processing speed interacts with working memory efficiency in multiple sclerosis. *Archives of Clinical Neuropsychology*, *21*, 229–238.

Lezak, M.D. (2012). *Neuropsychological assessment*. New York: Oxford University Press.

Libon, D.J., Glosser, G., Malamut, B.L., Kaplan, E., Goldberg, E., Swenson, R., & Prouty Sands, L. (1994). Age, executive functions, and visuospatial functioning in healthy older adults. *Neuropsychology*, *8*(1), 38.

Litvan, I., Grafman, J., Vendrell, P., Martinez, J.M., Junqué, C., Vendrell, J.M., & Barraquer-Bordas, J.L. (1988). Multiple memory deficits in patients with multiple sclerosis: Exploring the working memory system. *Archives of Neurology*, *45*, 607–610.

Lokken, K., Ferraro, F.R., Petros, T., Bergloft, P., Thompson, S., & Teetzen, M. (1999). The effect of importance level, delay, and rate of forgetting on prose recall in multiple sclerosis. *Applied Neuropsychology*, *6*, 147–153.

Lynch, S.G., Dickerson, K.J., & Denney, D.R. (2010). Evaluating processing speed in multiple sclerosis: A comparison of two rapid serial processing measures. *The Clinical Neuropsychologist*, *24*, 963–976.

Macniven, J.A. B., Davis, C., Ho, M.-Y., Bradshaw, C.M., Szabadi, E., & Constantinescu, C.S. (2008). Stroop performance in multiple sclerosis: Information processing, selective attention, or executive functioning? *Journal of the International Neuropsychological Society*, *14*, 805–814.

Matthews, C.G., Cleeland, C.S., & Hopper, C.L. (1970). Neuropsychological patterns in multiple sclerosis. *Diseases of the Nervous System, 31,* 161–170.

Mattioli, F., Bellomi, F., Stampatori, C., Capra, R., & Miniussi, C. (2016a). Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. *Multiple Sclerosis Journal*, *22*, 222–230.

Mattioli, F., Bellomi, F., Stampatori, C., Provinciali, L., Compagnucci, L., Uccelli, A., ... Pattini, M. (2016b). Two years follow up of domain specific cognitive training in relapsing remitting multiple sclerosis: A randomized clinical trial. *Frontiers in Behavioral Neuroscience*, *10.* DOI: 10.3389/fnbeh.2016.00028.

McIntosh-Michaelis, S.A., Roberts, M.H., Wilkinson, S.M., Diamond, I.D., McLellan, D.L., Martin, J.P., & Spackman, A.J. (1991). The prevalence of cognitive impairment in a community survey of multiple sclerosis. *British Journal of Clinical Psychology*, *30*, 333–348.

McNicholas, N., & McGuigan, C. (2016). A useful annual review of cognition in relapsing MS is beyond most neurologists–YES. *Multiple Sclerosis Journal*, *22*, 726–728.

Metzler, P. (2000). *Standardisierte Link'sche Probe zur Beurteilung exekutiver Funktionen: SLP (Standardized Link's Probe).* Frankfurt a.M. Swets Test Service.

Minden, S.L., Moes, E.J., Orav, J., Kaplan, E., & Reich, P. (1990). Memory impairment in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *12*, 566–586.

Minden, S.L., & Schiffer, R.B. (1991). Depression and mood disorders in multiple sclerosis. *Cognitive and Behavioral Neurology*, *4*, 62–77.

Möller, A., Wiedemann, G., Rohde, U., Backmund, H., & Sonntag, A. (1994). Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis. *Acta Psychiatrica Scandinavica*, *89*, 117–121.

Moreno, M.J. G., García, M.C., Marasescu, R., González, A.P., & Benito, Y.A. (2013). Neuropsychological syndromes in multiple sclerosis. *Psicothema*, *25*, 452–460.

Müller, S., Saur, R., Greve, B., Melms, A., Hautzinger, M., Fallgatter, A.J., & Leyhe, T. (2013). Similar autobiographical memory impairment in long-term secondary progressive multiple sclerosis and Alzheimer's disease. *Multiple Sclerosis Journal*, *19*, 225–232.

Niccolai, C., Portaccio, E., Goretti, B., Hakiki, B., Giannini, M., Pastò, L., ... Martinelli, V. (2015). A comparison of the brief international cognitive assessment for multiple sclerosis and the brief repeatable battery in multiple sclerosis patients. *BMC Neurology*, *15*(1), 204.

Niemann, H., Sturm, W., Thöne-Otto, A.I., & Willmes, K. (2008). *CVLT California verbal learning test. German adaptation. Manual*. Frankfurt a.M.: Pearson.

Nocentini, U., Bozzali, M., Spanò, B., Cercignani, M., Serra, L., Basile, B., ... De Luca, J. (2014). Exploration of the relationships between regional grey matter atrophy and cognition in multiple sclerosis. *Brain Imaging and Behavior*, *8*, 378–386.

Olivares, T., Nieto, A., Sánchez, M.P., Wollmann, T., Hernández, M.A., & Barroso, J. (2005). Pattern of neuropsychological impairment in the early phase of relapsing-remitting multiple sclerosis. *Multiple Sclerosis*, *11*, 191–197.

Osterrieth, P.A. (1944). Le test de copie d'une figure complexe (Test on copying a complex figure). *Archives of Psychology*, *30*, 206–356.

Owens, E.M., Denney, D.R., & Lynch, S.G. (2013). Difficulties in planning among patients with multiple sclerosis: A relative consequence of deficits in information processing speed. *Journal of the International Neuropsychological Society*, *19*, 613–620.

Papadopoulos, D., Dukes, S., Patel, R., Nicholas, R., Vora, A., & Reynolds, R. (2009). Substantial archaeocortical atrophy and neuronal loss in multiple sclerosis. *Brain Pathology*, *19*, 238–253.

Parmenter, B.A., Shucard, J.L., & Shucard, D.W. (2007a). Information processing deficits in multiple sclerosis: A matter of complexity. *Journal of the International Neuropsychological Society*, *13*, 417–423.

Parmenter, B.A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R.H. (2007b). Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Multiple Sclerosis Journal*, *13*, 52–57.

Parmenter, B.A., Zivadinov, R., Kerenyi, L., Gavett, R., Weinstock-Guttman, B., Dwyer, M.G., ... Benedict, R.H. (2007c). Validity of the Wisconsin card sorting and Delis–Kaplan executive function system (DKEFS) sorting tests in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *29*, 215–223.

Patti, F., De Stefano, M., Lavorgna, L., Messina, S., Chisari, C.G., Ippolito, D., ... Valentino, P. (2015). Lesion load may predict long-term cognitive dysfunction in multiple sclerosis patients. *PloS one*, *10*(3), e0120754.

Pelosi, L., Geesken, J.M., Holly, M., Hayward, M., & Blumhardt, L.D. (1997). Working memory impairment in early multiple sclerosis. Evidence from an event-related potential study of patients with clinically isolated myelopathy. *Brain*, *120*, 2039–2058.

Penner, I.-K., Rausch, M., Hardmeier, M., Kappos, L., & Radü, E.-W. (2001). Altered functional activation in MS patients with reduced attentional performance demonstrated with functional MRI. *Neuroimage*, *13*, 347.

Penner, I.-K., & Calabrese, P. (2007). Kognitive Störungen und Fatigue bei Patienten mit Multipler Sklerose: Über den Einsatz subjektiver und objektiver Screeningverfahren (Cognitive deficits and fatigue in patients with MS-application of subjective and objective screening instruments). *psychoneuro*, *33*, 508–515.

Penner, I.K., Raselli, C., Stöcklin, M., Opwis, K., Kappos, L., & Calabrese, P. (2009). The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple Sclerosis*, *15*, 1509–1517.

Penner, I.-K., Kandziora, P., Poettgen, J., Heesen, C., Lang, M., & Schreiber, H. (2015). German Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (P5. 196). *Neurology*, *84*(14 Supplement), P5. 196.

Peschke, V. (2004). Burgauer bedside screening. URL: www.psydat.de.

Peyser, J.M., Rao, S.M., LaRocca, N.G., & Kaplan, E. (1990). Guidelines for neuropsychological research in multiple sclerosis. *Archives of Neurology*, *47*, 94–97.

Piras, M.R., Magnano, I., Canu, E.D. G., Paulus, K.S., Satta, W.M., Soddu, A., … Aiello, I. (2003). Longitudinal study of cognitive dysfunction in multiple sclerosis: Neuropsychological, neuroradiological, and neurophysiological findings. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*, 878–885.

Plohmann, A.M., Kappos, L., Ammann, W., Thordai, A., Wittwer, A., Huber, S., … Lechner-Scott, J. (1998). Computer assisted retraining of attentional impairments in patients with multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *64*, 455–462.

Porcel, J., & Montalban, X. (2006). Anticholinesterasics in the treatment of cognitive impairment in multiple sclerosis. *Journal of the Neurological Sciences*, *245*(1), 177–181.

Portaccio, E., Goretti, B., Zipoli, V., Siracusa, G., Sorbi, S., & Amato, M.P. (2009). A short version of Rao's Brief Repeatable Battery as a screening tool for cognitive impairment in multiple sclerosis. *The Clinical Neuropsychologist*, *23*, 268–275.

Portaccio, E., Goretti, B., Zipoli, V., Iudice, A., Pina, D.D., Malentacchi, G.M., … Mazzoni, M. (2010). Reliability, practice effects, and change indices for Rao's Brief Repeatable Battery. *Multiple Sclerosis Journal*, *16*, 611–617.

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*(1), 25–42.

Potagas, C., Giogkaraki, E., Koutsis, G., Mandellos, D., Tsirempolou, E., Sfagos, C., & Vassilopoulos, D. (2008). Cognitive impairment in different MS subtypes and clinically isolated syndromes. *Journal of the Neurological Sciences*, *267*(1), 100–106.

Pöttgen, J., Lau, S., Penner, I., Heesen, C., & Moritz, S. (2015a). Managing neuropsychological impairment in multiple sclerosis: Pilot study on a standardized metacognitive intervention. *International Journal of MS Care*, *17*, 130–137.

Pöttgen, J., Stephan, J., Gold, S.M., Heesen, C., & Penner, I.-K. (2015b). Perceived and objective attentional deficits in multiple sclerosis. *Zeitschrift für Neuropsychologie, 26,* 171–178.

Pozzilli, C., Bastianello, S., Padovani, A., Passafiume, D., Millefiorini, E., Bozzao, L., & Fieschi, C. (1991). Anterior corpus callosum atrophy and verbal fluency in multiple sclerosis. *Cortex*, *27*, 441–445.

Prakash, R.S., Snook, E.M., Lewis, J.M., Motl, R.W., & Kramer, A.F. (2008). Cognitive impairments in relapsing-remitting multiple sclerosis: A meta-analysis. *Multiple Sclerosis Journal*, *14*, 1250–1261.

Pujol, J., Vendrell, P., Deus, J., Junqué, C., Bello, J., Martı-Vilalta, J.L., & Capdevila, A. (2001). The effect of medial frontal and posterior parietal demyelinating lesions on Stroop interference. *Neuroimage*, *13*, 68–75.

Radomski, A.D., Power, C., Purdon, S.E., Emery, D.J., Blevins, G., Warren, K.G., & Fujiwara, E. (2015). Decision-making under explicit risk is impaired in multiple sclerosis: Relationships with ventricular width and disease disability. *BMC Neurology*, *15*(1), 61–74.

Rao, S.M., Hammeke, T.A., McQuillen, M.P., Khatri, B.O., & Lloyd, D. (1984). Memory disturbance in chronic progressive multiple sclerosis. *Archives of neurology*, *41*, 625–631.

Rao, S.M., Hammeke, T.A., & Speech, T.J. (1987). Wisconsin Card Sorting Test performance in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of Consulting and Clinical Psychology*, *55*, 263–265.

Rao, S.M., Leo, G.J., & Aubin-Faubert, P.S. (1989a). On the nature of memory disturbance in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *11*, 699–712.

Rao, S.M., Leo, G.J., Haughton, V.M., Aubin-Faubert, P.S., & Bernardin, L. (1989b). Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology*, *39*, 161–161.

Rao, S.M. (1990a). *A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis.* Milwaukee: Medical College of Wisconsin.

Rao, S.M. (1990b). *Neurobehavioral aspects of multiple sclerosis*. New York: Oxford University Press.

Rao, S.M., Leo, G.J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis, I: Frequency, patterns, and prediction. *Neurology*, *41*, 685–691.

Rao, S.M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G.J., … Unverzagt, F. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology*, *7*, 364.

Raven, J.C. (1936). *Mental tests used in genetic studies: The performance of related individuals on tests mainly educative and mainly reproductive.* Unpublished master's thesis, University of London.

Regard, M., Strauss, E., & Knapp, P. (1982). Children's production on verbal and nonverbal fluency tasks. *Perceptual and Motor Skills*, *55*, 839–844.

Reitan, R.M. (1955). The relationship of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology*, *19*, 393–394.

Reitan, R.M., Reed, J.C., & Dyken, M.L. (1971). Cognitive, psychomotor, and motor correlates of multiple sclerosis. *The Journal of Nervous and Mental Disease*, *153*, 218–224.

Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique (Les problems). The psychological examination in cases of traumatic encephalopathy. *Archives de psychologie, 28,* 215–289.

Ricker, J.H., Axelrod, B.N., & Houtler, B.D. (1996). Clinical validation of the Oral Trail Making Test. *Cognitive and Behavioral Neurology*, *9*, 50–53.

Rocca, M.A., Valsasina, P., Absinta, M., Riccitelli, G., Rodegher, M.E., Misci, P., … Filippi, M. (2010). Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology*, *74*, 1252–1259.

Rocca, M.A., Amato, M.P., De Stefano, N., Enzinger, C., Geurts, J.J., Penner, I.-K., … Filippi, M. (2015). Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *The Lancet Neurology*, *14*, 302–317.

Rogers, J.M., & Panegyres, P.K. (2007). Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. *Journal of Clinical Neuroscience*, *14*, 919–927.

Ron, M.A., Callanan, M.M., & Warrington, e.K. (1991). Cognitive abnormalities in multiple sclerosis: A psychometric and MRI study. *Psychological Medicine*, *21*, 59–68.

Rosti, E., Hämäläinen, P., Koivisto, K., & Hokkanen, L. (2007). PASAT in detecting cognitive impairment in relapsing-remitting MS. *Applied neuropsychology*, *14*, 101–112.

Ruff, R.M., Light, R.H., & Evans, R.W. (1987). The Ruff Figural Fluency Test: A normative study with adults. *Developmental Neuropsychology*, *3*, 37–51.

Ryan, L., Clark, C.M., Klonoff, H., Li, D., & Paty, D. (1996). Patterns of cognitive impairment in relapsing-remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. *Neuropsychology*, *10*, 176–193.

Sanchez-Cubillo, I., Perianez, J.A., Adrover-Roig, D., Rodriguez-Sanchez, J.M., Rios-Lago, M., Tirapu, J., & Barcelo, F. (2009). Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society*, *15*, 438–450.

Sandry, J., Paxton, J., & Sumowski, J.F. (2016). General mathematical ability predicts PASAT performance in ms patients: Implications for clinical interpretation and cognitive reserve. *Journal of the International Neuropsychological Society*, *22*, 375–378.

Savettieri, G., Messina, D., Andreoli, V., Bonavita, S., Caltagirone, C., Cittadella, R., … Le Pira, F. (2004). Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis. *Journal of Neurology*, *251*, 1208–1214.

Schale, A., & Küst, J. (2009). Fahreignung nach Hirnschädigung. In Sturm, W., Hermann, M., Münte, T.F. (Ed.) *Lehrbuch der klinischen Neuropsychologie. Grundlagen, Methodik, Diagnostik, Therapie* (pp. 341–351). Heidelberg: Spektrum.

Scherer, P., Penner, I.K., Rohr, A., Boldt, H., Ringel, I., Wilke-Burger, H., … Zahrnt, S. (2007). The Faces Symbol Test, a newly developed screening instrument to assess cognitive decline related to multiple sclerosis: First results of the Berlin Multi-Centre FST Validation Study. *Multiple Sclerosis Journal*, *13*, 402–411.

Schretlen, D., Bobholz, J.H., & Brandt, J. (1996). Development and psychometric properties of the Brief Test of Attention. *The Clinical Neuropsychologist*, *10*, 80–89.

Schuhfried, G. (1992). *Vienna reaction unit (manual).* Austria: Schuhfried.

Schultheis, M.T., Garay, E., & DeLuca, J. (2001). The influence of cognitive impairment on driving performance in multiple sclerosis. *Neurology*, *56*, 1089–1094.

Schulz, D., Kopp, B., Kunkel, A., & Faiss, J.H. (2006). Cognition in the early stage of multiple sclerosis. *Journal of Neurology*, *253*, 1002–1010.

Shah, A. (2009). Fatigue in multiple sclerosis. *Physical medicine and rehabilitation clinics of North America*, *20*, 363–372.

Sherman, T.E., Rapport, L.J., & Ryan, K.A. (2008). Awareness of deficit in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *30*, 301–311.

Shum, D.h., McFarland, K.A., & Bain, J.D. (1990). Construct validity of eight tests of attention: Comparison of normal and closed head injured samples. *The Clinical Neuropsychologist*, *4*, 151–162.

Sicotte, N.L., Kern, K.C., Giesser, B.S., Arshanapalli, A., Schultz, A., Montag, M., … Bookheimer, S.Y. (2008). Regional hippocampal atrophy in multiple sclerosis. *Brain*, *131*, 1134–1141.

Smith, A. (1982). Symbol digit modalities test (SDMT) manual (revised). Western Psychological Services. *Los Angeles*.

Sonder, J.M., Burggraaff, J., Knol, D.L., Polman, C.H., & Uitdehaag, B.M. (2014). Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Multiple Sclerosis Journal*, *20*, 481–488.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., … Ladurner, G. (2002). Cognitive function and fMRI in patients with multiple sclerosis: Evidence for compensatory cortical activation during an attention task. *Brain*, *125*, 1275–1282.

Stegen, S., Stepanov, I., Cookfair, D., Schwartz, E., Hojnacki, D., Weinstock-Guttman, B., & Benedict, R.H. (2010). Validity of the California Verbal Learning Test–II in multiple sclerosis. *The Clinical Neuropsychologist*, *24*, 189–202.

Strauss, E., Sherman, E.M., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. New York: Oxford University Press. American Chemical Society.

Strober, L., Englert, J., Munschauer, F., Weinstock-Guttman, B., Rao, S., & Benedict, R.H. B. (2009). Sensitivity of conventional memory tests in multiple sclerosis: Comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. *Multiple Sclerosis Journal*, *15*, 1077–1084.

Stuss, D.T., Bisschop, S.M., Alexander, M.P., Levine, B., Katz, D., & Izukawa, D. (2001). The Trail Making Test: A study in focal lesion patients. *Psychological Assessment*, *13*, 230.

Swirsky-Sacchetti, T., Mitchell, D.R., Seward, J., Gonzales, C., Lublin, F., Knobler, R., & Field, H.L. (1992). Neuropsychological and structural brain lesions in multiple sclerosis: A regional analysis. *Neurology*, *42*, 1291–1291.

Thornton, A.E., & Raz, N. (1997). *Memory impairment in multiple sclerosis: A quantitative review.* Washington, DC: American Psychological Association.

Tinelli, E., Francia, A., Quartuccio, E.M., Morreale, M., Contessa, G.M., Pascucci, S., … Pantano, P. (2013). Structural brain MR imaging changes associated with obsessive-compulsive disorder in patients with multiple sclerosis. *American Journal of Neuroradiology*, *34*, 305–309.

Tombaugh, T.N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*, 203–214.

Tröster, A.I., Fields, J.A., Testa, J.A., Paul, R.H., Blanco, C.R., Hames, K.A., … Beatty, W.W. (1998). Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. *Neuropsychologia*, *36*, 295–304.

Tucha, O., & Lange, K.W. (2004). *Turm von London: Deutsche Version, TL-D (Tower of London)*. Göttingen: Hogrefe.

Vacchi, L., Rocca, M.A., Meani, A., Rodegher, M., Martinelli, V., Comi, G., … Filippi, M. (2017). Working memory network dysfunction in relapse-onset multiple sclerosis phenotypes: A clinical-imaging evaluation. *Multiple Sclerosis Journal, 23,* 577–587

Van den Burg, W., Van Zomeren, A.H., Minderhoud, J.M., Prange, A.J., & Meijer, N.S. (1987). Cognitive impairment in patients with multiple sclerosis and mild physical disability. *Archives of Neurology*, *44*, 494–501.

Veiel, H.O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, *19*, 587–603.

Vleugels, L., Lafosse, C., van Nunen, A. n, Nachtergaele, S., Ketelaer, P., Charlier, M., & Vandenbussche, E. (2000). Visuoperceptual impairment in multiple sclerosis patients diagnosed with neuropsychological tasks. *Multiple Sclerosis Journal*, *6*, 241–254.

Vogt, A., Kappos, L., Calabrese, P., Stöcklin, M., Gschwind, L., Opwis, K., & Penner, I.-K. (2009). Working memory training in patients with multiple sclerosis: Comparison of two different training schedules. *Restorative Neurology and Neuroscience*, *27*, 225–235.

Von Cramon, D.Y., & Matthes-von Cramon, G. (1993). Problemlösen des Denken. In: Von Cramon, D.Y., Mai, N., Ziegler, W. (Ed.) *Neuropsychologische Diagnostik.* Weinheim: VCH, 123–152.

Warrington, e.K., & James, M. (1991). *The visual object and space perception battery*. Bury St Edmunds: Thames Valley Test Company.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*. San Antonio, TX: Peason.

Wegener, S., Marx, I., & Zettl, U.K. (2013). Cognitive deficits and dementia in patients with multiple sclerosis: status quo and open questions. *Fortschritte der Neurologie-Psychiatrie*, *81*, 639–647.

Williams, J., O'Rourke, K., Hutchinson, M., & Tubridy, N. (2006). The face-symbol test and the symbol-digit test are not reliable surrogates for the Paced Auditory Serial Addition Test in multiple sclerosis. *Multiple Sclerosis Journal*, *12*, 599–604.

Zakzanis, K.K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. *Archives of Clinical Neuropsychology*, *15*, 115–136.

Zimmermann, P., & Fimm, B. (2009). *Testbatterie zur Aufmerksamkeitsprüfung-Version 2.2:(TAP) [Handbuch] (Test battery of attentional performance).* Herzogenrath: Psytest.

Appendix 1. List of Abbreviations in Alphabetical Order

ADS	Allgemeine Depressionsskala
ANT	Attention Network Test
APM	Advanced Progressive Matrices
BDI2	Beck-Depressionsinventar

BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
B-kPT	Burgauer kleiner Planungstest
BRB	Brief Repeatable Battery
BTA	Brief Test of Attention
BVMT	Brief Visuospatial Memory Test – Revised
CCST	California Card Sorting Test
CIS	Clinically Isolated Syndrome
CLTR	consistent long-term retrieval
CNS	Central Nervous System
COWAT	Controlled Oral Word Association Test
CPMS	Chronic-progressive Multiple Sclerosis
CVLT	California Verbal Learning Test
D-KEFS	Delis-Kaplan Executive Function Score
EDSS	Expanded Disability Status Scale
FPT	Five Point Test
FRT	Facial Recognition Test
FST	Faces Symbol Test
IPS	information processing speed
ISI	interstimulus-interval
JLO	Judgment of Line Orientation Test
LTS	long-term storage
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis
(f)MRI	(functional) magnetic resonance imaging
FSMC	Fatigue Scale for Motor and Cognitive Functions
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire
NSB	Neuropsychological Screening Battery
PASAT	Paced Auditory Serial Addition Test
PVSAT	Paced Visual Serial Addition Test
PPMS	Primary progressive Multiple Sclerosis
RFFT	Ruff Figural Fluency Test
ROCF	Rey-Osterrieth Complex Figure Test
RRMS	Relapsing-remitting Multiple Sclerosis
RWT	Regensburger Wortflüssigkeitstest
SLP	Standardisierte Link'sche Probe
SPMS	Secondary progressive Multiple Sclerosis
SDMT	Symbol Digit Modalities Test
SPM	Standard Progressive Matrices
SRT	Selective Reminding Test
ST	Stroop Test
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TMT	Trail Making Test
VFD	Visual Form Discrimination Test
VLMT	Verbal Learning and Memory Test
VOSP	Visual Object and Space Perception Battery
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WEIMUS	Würzburger Erschöpfungsinventar for Multiple Sclerosis
WLG	Word List Generation Task
WMS	Wechsler Memory Scale

Submitted: 13.05.2017
Accepted after revision: 15.05.2017
There are no conflicts of interest existing.

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CME-Questions

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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Fortbildungszertifikat

Die Ärztekammer Niedersachsen erkennt hiermit 1 Fortbildungspunkte an.

Stempel

Zeitschrift für Neuropsychologie 2 / 2017

hogrefe

Neuropsychological Assessment in Multiple Sclerosis

Die Antworten bitte deutlich ankreuzen!

	1	2	3	4	5
a	○	○	○	○	○
b	○	○	○	○	○
c	○	○	○	○	○
d	○	○	○	○	○
e	○	○	○	○	○

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

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