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ADVANCES IN MULTIPLE SCLEROSIS

Cognitive Issues in MULTIPLE SCLEROSIS

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IMSCOGS

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CME/CE Information

TARGET AUDIENCE

This activity is intended for neurologists, nurses, nurse practitioners, physician assistants, rehabilitation professionals, case managers, mental health professionals, social workers and others involved in the management of patients with MS.

LEARNING OBJECTIVES

Upon completion of the activity, participants should be able to:

- Recognize the vital importance of recognizing and treating cognitive impairment and related symptoms in MS patients with a goal of early intervention
- In collaboration with other members of the healthcare team, conduct an appropriate, comprehensive assessment of the patient's cognitive profile that incorporates both knowledge of the history of this symptom and information obtained through neuroimaging techniques
- Examine new MRI/psychometric correspondence data and current understanding of the importance of the patient's potential for cognitive reserve and its impact on potential progression and incorporate this information into long-term planning strategies for the management of cognitive change
- Work collaboratively with a team of related professionals and scientists to develop and disseminate best practices in the comprehensive management (e.g., assessment and rehabilitation) of cognitive impairment in multiple sclerosis

STATEMENT OF NEED

Diagnostic criteria exist for MS, yet data reveal the paucity of skills and competence needed to evaluate cognitive dysfunction in MS. Furthermore, although much progress has been made, the causes of cognitive dysfunction in MS remain to be fully elucidated. The most comprehensive neuropsychological assessment batteries have been demonstrated to be effective, but require administration by trained personnel and are quite costly and time-consuming. Furthermore, patients tend to be reluctant to bring up cognitive issues, and providers are not well-attuned to cues indicative of a need to investigate for the existence of a cognitive defect. Therefore, recent research has focused on the creation of new tools that can be easily and inexpensively implemented by the MS clinician. As a result of this research, these important and necessary tools now exist, but clinicians are either unaware of them or not familiar with their application.

In addition to assessment tools, there is emerging evidence about the effectiveness of rehabilitation to reduce the impact of impaired cognition. This information is vital to the health and well-being of those affected by MS. Cognition has been shown to be significantly associated with several MRI indices of brain structure and function, and is an important and active area of clinical research. MRI indices have also been useful in documenting change over time and response to rehabilitation.

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120 minutes

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1. There are no fees for participating in and receiving credit for this activity.
2. Review the activity objectives and CME/CE information.
3. Complete the CME/CE activity.
4. Go to **www.cmeAIMS.org/cognitive** and complete the posttest. A score of at least 75% is required to successfully complete this activity. The participant may take the test until successfully passed.
5. Complete the CME/CE evaluation/attestation form at **www.cmeAIMS.org/cognitive**, which provides each participant with the opportunity to comment on how participating in the activity will affect their professional practice; the quality of the instructional process; the perception of enhanced professional effectiveness; the perception of commercial bias; and his/her views on future educational needs.
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The faculty listed below report that they have no relevant financial relationships to disclose:

- **Christine Till, PhD, C.Psych**

The following faculty report that they have relevant financial relationships to disclose:

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- **John DeLuca, PhD,** has received honoraria from Biogen and has research contracts for Biogen.
- **Frederick W. Foley, PhD,** has received honoraria from Biogen.
- **Dawn Langdon, MA, PhD**, has received honoraria from Bayer, Novartis, and Teva and has been on the speakers bureau for Almirall, Bayer, Biogen, Exemed, Novartis, and Teva, and has research contracts with Bayer, Biogen, and Novartis.

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Forward

On behalf of the International Multiple Sclerosis Cognition Society (IMSCOGS) Executive Board, Program Chair, John DeLuca, PhD, and CMSC CEO, June Halper, I am proud to bring you this important primer on cognitive issues in multiple sclerosis. This primer summarizes information presented at the 5th Annual IMSCOGS Meeting, which took place June 23-24, 2016 in New York City.

The program for the meeting included sessions on neuropsychological assessment, cognition and the brain, cognitive interventions in MS, pediatric MS, how cognition influences everyday functional activity, cognition in progressive MS, and the effect of cannabis on cognition. Each of those topics is summarized here in an easy-to-follow primer format with an emphasis on evidence-based conclusions.

This year's meeting was unparalleled in the breadth of content related to MS neuropsychology, not to mention its supreme location, networking, and educational opportunities. We hope that this primer will become an invaluable resource to you, the clinician. You will now have detailed and concise information at your fingertips on the often overlooked issues related to the cognitive problems faced by MS patients. Whether you plan to read the primer cover-to-cover or use it as an as-needed reference source, we hope that you find it useful and informative.

We would appreciate hearing of your impression of this document. Please drop us a note to let us know your thoughts.

Dr. Ralph H. Benedict, PhD
President, IMSCOGS

Introduction

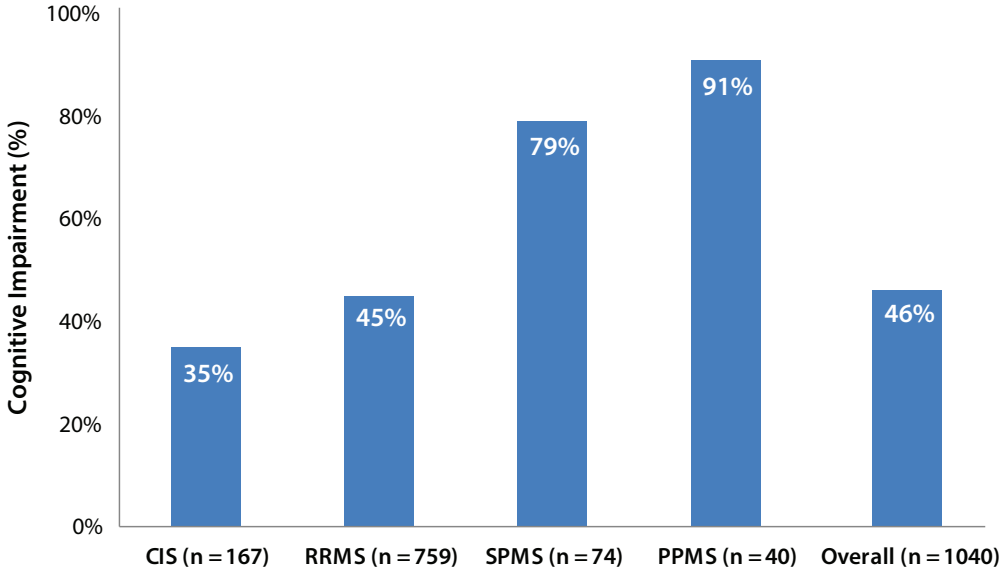
Faculty: John DeLuca, PhD

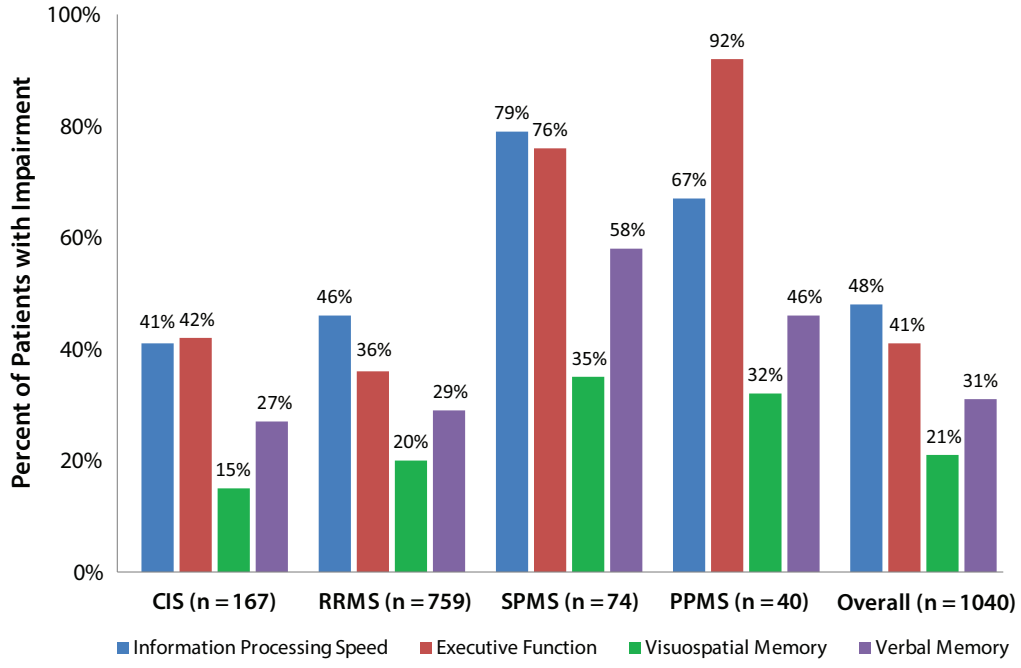
Cognitive changes are present in a significant proportion of individuals with multiple sclerosis (MS), and can have a dramatic impact on activities of daily living, vocational and social functioning, and disease management, as well as overall quality of life. The prevalence of cognitive impairment reported from studies varies depending on the patient population(s) studied, study design, and neuropsychological measures/outcomes. Reports in the literature range from 30-70%.[1,2] Commonly affected domains include speed of information processing, working memory, verbal and visual memory, complex attention, verbal fluency, theory of mind, and executive functions.

Cognitive impairment can be present in patients with clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), pediatric MS, and progressive forms of MS (PPMS and SPMS). It may be significant in patients with little-to-no physical disability. Conversely, some patients with high *Expanded Disability Status Score* (EDSS) scores may be cognitively preserved. A recent cross-sectional study reported by Ruano et al describes the prevalence and profile of cognitive impairment in a large sample of patients with MS from 6 Italian centers.[3] Neuropsychological assessments in this study included Rao's *Brief Repeatable Neuropsychological Battery* (BRB) and the *Stroop Test*. Overall, cognitive impairment was present in 46% of the patient population, with the highest prevalence in patients with SPMS and PPMS **(Figure 1, next page)**.[3] Neuropsychological profiles in this patient cohort varied by clinical subtype **(Figure 1)**, with impairment in information processing speed and executive functions the most commonly affected domains in this sample. Multivariate regression analysis demonstrated that age and EDSS were significantly correlated with cognitive impairment in this study (OR 1.62 [1.42, 1.86], $P < 0.001$; and OR 1.80 [1.51, 2.15], $P < 0.001$, respectively).[3] Interestingly, a cross sectional study of 135 patients with CIS or early RRMS reported three cognitive profile clusters based on performance on the BRB.[4] The authors reported that the majority of this patient sample performed within the normal range on all cognitive domains tested; ~16% of the sample exhibited deficits only on tests of information processing speed; and 9% of patients performed lower than average on all cognitive domains.[4] Celius et al have conducted 25-year follow-up of a cohort of MS patients who were part of the Oslo MS-registry and showed that impaired cognition as assessed by *Symbol Digit Modalities Test* (SDMT) and *Paced Auditory Serial Addition Test* (PASAT) early in the disease was associated with shorter survival.[5] While based on a small sample size, this study suggests that impaired cognition at disease onset may indicate a more severe disease course.[5]

This publication contains a comprehensive summary of presentations on cognitive issues in MS from the 5th Meeting of the International Multiple Sclerosis Cognition Society (IMSCOGS), which was held in New York, New York on June 23-24, 2016.

Figure 1: Cognitive Impairment in Patients with MS from 6 Italian Centers[3]





Assessment of Cognition in MS

Faculty: Dawn Langdon, PhD

The prevalence of cognitive impairment in the MS population combined with the significant impact of cognitive changes on quality of life provide compelling reasons to perform assessment of cognition in this patient population. While significant others and care-givers may provide important information regarding the cognitive status of loved ones with MS, patient self-reports are generally not consistent with objective evaluation, and cognitive deficits may be difficult to discern during a routine neurological examination.[6,7] A number of neuropsychological assessment tools have been utilized for the MS population, several of which are summarized in Table 1.

Until recently, the most widely used and validated batteries for MS were the Rao *Brief Repeatable Neuropsychological Battery* (BRB)[8] and the Minimal Assessment of Cognitive Function in MS (MACFIMS).[9] These batteries are similar, but differ in the tests for visual/spatial, memory and executive function domains. MACFIMS, which was developed following a consensus meeting in 2001, is a 90-minute battery covering five commonly impacted cognitive domains in persons with MS. Since the introduction of MACFIMS, considerable research has accumulated showing that this battery is sensitive to separating patients with MS from healthy controls, has good test/retest reliability,

Table 1: Neuropsychological Batteries for Patients with MS

Cognitive Domain	Rao Brief Repeatable Neuropsychological Battery (BRB)[8]	Minimal Assessment of Cognitive Function in MS (MACFIMS)[9]	NINDS Common Data Elements[10]	MS-COG[11]	Brief Cognitive Assessment of Multiple Sclerosis (BICAMS)[12]
Cognitive Processing Speed	SDMT	SDMT	SDMT	SDMT	SDMT
	PASAT	PASAT	PASAT	PASAT	
Language	COWAT	COWAT	COWAT		
Visual/Spatial		JLO			
Memory	SRT	CVLT2	CVLT2	SRT	CVLT2
	10/36 Spatial Recall Test	BVMTR	BVMTR	BVMTR	BVMTR
Executive Function		DKEFS	DKEFS		

NINDS: National Institute of Neurological Disorders and Stroke; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation Test; SRT: Selective Reminding Test; CVLT2: California Verbal Learning Test 2nd Edition; BVMTR: Brief Visuospatial Memory Test, Revised; DKEFS: Delis-Kaplan Executive Function System Sorting Test. With permission of Ralph HB Benedict, PhD.

ecological validity, and regression-based norms are available for interpretation.[13,14] While both the BRB and MACFIMS are characterized by reliable psychometric properties, they are time consuming (45 and 90 minutes, respectively), and not applicable to routine clinical practice (specialized training or access to neuropsychologists is needed for administration and scoring/interpretation of tests). These limitations led to the development of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).[12] The goals for the development of BICAMS included identification of a brief assessment tool for cognition in MS that can be used by health care professionals who are not cognitive specialists (and therefore is applicable to routine clinical practice); a tool that has international validation, where an international validation protocol can be specified and implemented in any country; and guidelines can be agreed upon for test-retest timing and clinically significant change. Tests identified for inclusion in BICAMS are: SDMT for information processing speed; CVLT2 (T1-5) for verbal memory (immediate recall); and BVMTR (T1-3) for visual memory (immediate recall).[12] The recommended order for test administration is SDMT, followed by CVLT2, and then BVMTR.

Niccolai et al recently published a study comparing the performance of BICAMS and BRB in MS patients from 11 Italian MS centers.[15] All tests included in the batteries separated healthy controls and MS patients, with moderate accord between BRB and BICAMS (Cohen's K statistic, 0.46).[15] Cohen's d for each of the tests included in BICAMS were 0.83 for SDMT, 0.61 for CVLT2, and 0.60 for BVMTR.[15] In routine practice, the 3 tests included in BICAMS have been shown to correlate with MRI findings.[16] Mike et al conducted a study investigating the frequency of cortical lesions and relationships to white matter lesions and cognitive and physical disability. Twenty-five patients completed the MACFIMS battery, and SDMT was shown to correlate with cortical lesion number and volume and white matter lesion volume; CVLT2 correlated with cortical lesion number; and BVMTR correlated with cortical lesion volume and white matter lesion volume. In multivariate testing after correction for age, depression and pre-morbid intelligence, the SDMT correlated with cortical lesion number and volume, and white matter lesion volume; and CVLT2 correlated with cortical lesion number.[16] Goverover et al examined whether BICAMS can predict performance of activities of daily living in persons with MS.[17] In this study of 41 individuals with MS and 32 healthy controls, the authors showed that better BICAMS performance was associated with more independent actual reality task performance (accessing the internet to purchase an airplane ticket or cookies). In addition, the authors reported that self-reports were not correlated with either performance of actual reality tasks or BICAMS outcomes.[17]

One of the goals with the development of BICAMS was to extend the use of this assessment tool to as many parts of the world as possible, and thereby facilitate comparison of data sets internationally. International standards for validation have been proposed including:

1. Standardize test stimuli for the target culture or language
2. Examiner instructions must be standardized and translated
3. Study of at least 65 healthy persons for normalization
4. Assessment of test-retest reliability (MS patients and healthy volunteers, test administration separated by 1-3 weeks)
5. Establish criterion-related validity (MS patients vs. healthy controls).[18]

There is an extensive international BICAMS validation pipeline, with studies published in at least 10 countries, and more in progress **(Table 2)**.

To date, data have been published with BICAMS from over 800 healthy controls and over 800 patients with MS.[27] Review of data obtained from different countries shows that the levels of cognitive impairment using BICAMS are very similar, ranging from 52% to 58% of persons with MS failing at least one BICAMS test.

Table 2: BICAMS National Validation Pipeline[19-26]

Discussions	Planning	Data Collection Ongoing	Presented	Published
Sweden	Spain	Russia	Turkey	US
Ukraine	Denmark	France	UK	Persia
	Japan	Romania	Greece	Czech Republic
		Germany		Italy
		Latvia		Hungary
		Belgium		Brazil
		Portugal		Ireland
		Estonia		Canada
				Argentina
				Lithuania

BICAMS has a website, which is freely available to anyone in the health care profession (www.BICAMS.net).[28] There are currently 130 centers contributing data to the website (150 regular visitors), with 1,400 patients in the database, and geographic representation is mainly from the US, UK, and the EU. An iPad version of BICAMS is currently in development.

Obtaining a baseline assessment of cognitive status in persons with MS followed by routine assessment every 1-2 years, or as needed with signs of a clinical relapse or problem could greatly enhance the management and support of these patients. BICAMS is conducive to routine use in clinical practice. Advantages of using BICAMS for annual assessment are summarized in **Table 3.**

Routine assessment of cognitive status in patients with MS has been recommended by the National Institute for Health and Care Excellence (NICE) in the UK,[29,30] and this approach has been included in the American Academy of Neurology quality measurement set for MS.[31] A recent study conducted in Germany evaluated the use of BICAMS in daily clinical practice of neurologists in private practices.[32] This study, with data from 1,547 patients and 59 practices, supported the feasibility of using BICAMS in routine clinical practice,

Table 3: Advantages Associated with Use of BICAMS for Annual Assessment of MS Patients

- Patients with discrepantly low function can be assessed for cognitive dysfunction versus fatigue or depression
- Patients with cognitive problems can be appropriately managed and monitored
- Information can be provided to patients in a way that is suitable and best assimilated
- The effects of cognitive impairment can be considered with regard to symptom management, medication adherence, fall risk, driving risk, and employment risk
- Specialists can be engaged as necessary for additional assessment and particular management and/or rehabilitation needs

however the authors note the importance of careful training of staff involved in the performance and scoring of the neuropsychological tests.[32]

Other approaches to cognitive assessment for persons with MS have recently been reported. Gromisch et al evaluated highly abbreviated measures from the MACFIMS (1-2 trials of BVMTR, SDMT, DKEFS, and COWAT).[33] Rao et al have reported an iPad-based tool for assessing cognitive dysfunction (Processing Speed Test), which can be self-administered and completed in the waiting room.[34] Virtual reality environments and actual reality tests have been developed, which demonstrate good separation of MS patients from healthy controls on selected tasks and tests.[17,35]

It is important to note that clinicians should be mindful of disease-specific considerations related to assessment of cognitive status in persons with MS. Physical symptoms can potentially confound outcomes depending on the assessment tool employed. For example, dysarthria can negatively impact tests in which a spoken response is required and/or timed. Pain, fatigue, anxiety or depression may affect performance on cognitive measures, and there are advantages to measuring these symptoms at each time cognitive assessment is performed.

Cognition is recognized as an important dimension of clinically meaningful disability in MS. The Multiple Sclerosis Outcome Assessment Consortium (MSOAC) has a mission to evaluate clinical trial data to qualify a new clinical outcome measure for disability in MS clinical trials.[36-38] This measure will be qualified by the FDA and EMA for future use as a primary or secondary endpoint of disability in future clinical trials of MS therapies. Domains reflecting common problems for persons with MS will be included: visual function, ambulation, coordination/upper extremity function, and cognition. The SDMT will be included for the assessment of cognition, a test with a long history associated with evaluation of information processing speed.[39] A recent meta-analysis of several of the commonly used neuropsychological tests in standard batteries showed that the SDMT had the highest effect size (Cohen's d, SDMT, 1.11; PASAT, 0.63; BVMTR, 1.03; CVLT2, 0.89; SRT, 0.86, and COWAT, 0.54).[40]

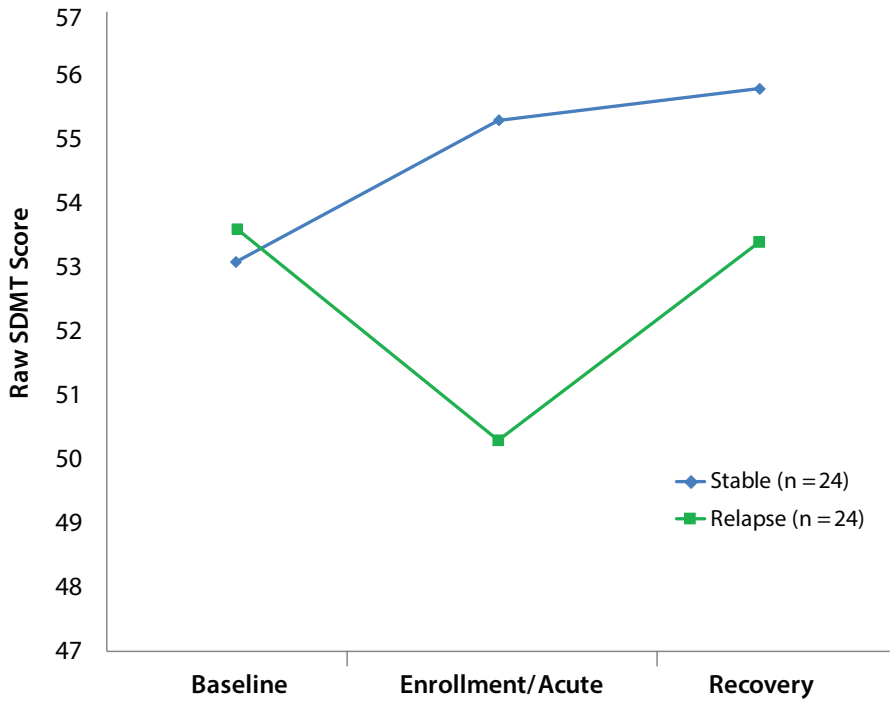
As with any clinical outcome measure, statistically significant change in an endpoint may not correlate with *clinically meaningful* change. For neuropsychological testing, determining clinically meaningful change (for example with the SDMT) is particularly challenging when the outcomes do not directly translate to everyday activities.[41] Benedict et al examined neurocognitive status in patients with MS before, during, and after a relapse compared with individually-matched stable patients.[42] Relapsing patients were required to have clinical symptoms consistent with a relapse and mental status changes per patient or caregiver report or clinician observation; enhancing MRI lesions provided confirmation of relapse. This analysis, which included 24 relapsing patients and 24 matched stable MS patients, showed that the groups were well matched with SDMT scores at baseline, but SDMT fell significantly with relapse ($P = 0.005$), compared with a slight increase in stable controls **(Figure 2, next page)**. At 3 months recovery following relapse, the SDMT scores in the relapse group had returned close to baseline values.

Consistent with the 3.5 point decline on SDMT in this study, Morrow et al have proposed a 3-4 point change in raw SDMT score as a threshold for clinical meaningfulness.[43]

Benedict et al recently conducted a study to link component tests of BICAMS and the MS Functional Composite with functional impairment based on vocational disability.[44] This study included data for 275 MS patients and 109 healthy controls. Study participants were separated into groups based on work status: MS work disabled, MS work challenged, MS work stable and healthy control work stable. Benchmark values were distinguished for each of the performance tests (timed 25-foot walk, CVLT2, SDMT, 9-hole peg test, BVMTR, and PASAT) by anchor group, with significant differences across all

levels of work status. For the SDMT, the test means ± standard deviation by vocational group were: MS work disabled, 45 ± 13; MS work challenged, 55 ± 11; MS work stable, 60 ± 12; and healthy control work stable, 63 ± 10.[44] SDMT and the timed 25-foot walk test were found to be the most discriminating cognitive and motor tasks, respectively, in this analysis.[44]

Figure 2: SDMT Scores: Relapsing vs. Stable Patients (adapted)[42]



Structural and Functional Correlates of Cognitive Impairment in MS

Faculty: Maria A. Rocca, MD

Magnetic resonance imaging (MRI) has been formally included in the diagnostic workup of MS patients in 2001, with the McDonald diagnostic criteria.[45] MRI is also a valuable tool for monitoring MS disease activity and progression, providing quantitative information on inflammatory activity and lesion load. While a number of studies have reported an association between lesion burden and neuropsychological performance, other reports indicate only a modest association between T2 lesions of the whole brain or specific sites in white matter and performance on neuropsychological tests.[46] Variability in study results looking at white matter lesions and cognitive performance may in part be due to differences in patient populations studied, sample sizes, neuropsychological tests utilized, criteria used for definition of cognitive impairment, methods for MRI quantification of brain lesions, and statistical methods.[46] It is increasingly clear that from a structural perspective, assessment of white matter lesions alone is insufficient to explain cognitive changes in patients with MS; damage to normal appearing white matter (NAWM), cortical areas, and deep grey matter (GM) structures contribute to these deficits as well.[47,48] Advances in MRI techniques have provided opportunities to better understand subtle changes in the brains of patients with MS related to cognitive impairment and the heterogeneity of cognitive profiles in these patients. Table 4 includes a summary of advanced MRI techniques used for the MS patient population.

Table 4: Advanced MRI Techniques (adapted from Filippi et al[49])

Sequence	What is Measured	Advantages	Disadvantages	Setting of Use
Double Inversion Recovery (DIR) [suppression of WM and CSF by two inversion times]	Grey matter lesions quantification and topographic classification (leucortical, intracortical)	Superior contrast between GM/CSF and GM/WM than conventional sequences (FLAIR, PD/T2, and T1)	Not useful for detection of subpial cortical lesions; limited detection of intracortical lesions; prone to artifacts; low signal; not yet standardized	Research
Magnetization Transfer Ratio (MTR) [gradient-echo or spin-echo sequences with and without an off-resonance saturation pulse]	Quantitative index derived from magnetization transfer imaging; efficiency of the magnetization exchange between protons in tissue water (relatively free) and those bound to the macromolecules; sensitivity and specificity to myelin	Superior to conventional MRI for the detection and quantification of microscopic tissue abnormalities in the WM and GM	Inter-subject and inter-scanner variability; strong effect from water content; intercenter variability	Research, clinical trials

Table 4: Advanced MRI Techniques (*cont*)

Sequence	What is Measured	Advantages	Disadvantages	Setting of Use
High-resolution 3D T1-weighted Sequences	Quantification of degree and topography of atrophy (grey matter and white matter separately)	Highly reproducible; sensitive to longitudinal changes; availability of robust post-processing methods	"Late" biomarker sensitive to irreversible tissue loss	Research, clinical trials
Diffusion Tensor Imaging (DTI)	Quantitative measurements (fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity) of brain tissue microstructure obtained through exploitation of the properties of water diffusion	Sensitive to WM microstructural damage	Inter-subject and inter-scanner variability; additional investigations are warranted to elucidate the correlates with pathological damage	Research
Proton Spectroscopy (^{1}H-MRS)	Quantification of different metabolites in voxels of interest	High specificity (N-acetyl aspartate: axonal damage; choline and lactate: myelin damage and inflammation)	Technically challenging; acquisition protocol and post-processing analysis need to be standardized across centers	Research, clinical trials
Functional MRI (fMRI) [T2* gradient echo or T2 spin echo sequence]	Blood oxygen level dependent (BOLD) signal	Evaluation of cortical reorganization	Inter-subject and inter-session variability; analysis needs appropriate statistical methods	Research, feasible also in multicentric study

In 2002, Rovaris et al described results of an exploratory study assessing the magnitude of correlation between diffusion tensor imaging (DTI) results in patients with RRMS and measures of cognitive impairment.[50] The authors reported that DTI metrics reflected the severity of language, attention and memory deficits in the RRMS patient population studied (with moderate correlations). Their results also supported the contribution of damage of the NAWM and GM (in addition to macroscopic lesions) to neuropsychological deficits in these patients. DTI has also been used to look for changes in NAWM in a 12-week exploratory cognitive rehabilitation study of patients with RRMS.[51]

Deloire et al used magnetization transfer ratio (MTR) imaging to evaluate the underlying pathological basis of cognitive impairment in early RRMS.[52] In this study of 44 RRMS patients within 6 months of diagnosis and matched controls for age, sex, and education, patients displayed worse performance on tests of verbal and spatial memory, attention, information processing speed, inhibition and conceptualization. Multivariate regression analysis showed that NAWM MTR and lesion load

were significantly associated with deficits in attention and information processing speed in this patient group. These results suggest that even at early stages of MS, axonal degeneration within the intercortical networks may be contributing to cognitive deficits.[52]

Recently, Schoonheim et al investigated the relationship between WM damage and cognition in a large cohort of patients with MS at 6 years following diagnosis.[53] Using DTI, the extent and severity of damage of the WM skeleton was assessed and these measures were related to cognitive performance using a multivariate model. These authors showed that the extent of WM changes (abnormal fractional anisotropy), especially in the thalamus, was significantly related to cognitive performance. The extent and severity of WM changes were greater in males with MS in this cohort than females, even though the groups were not different with regard to disease duration, disability and WM lesion volume.[53]

Cross sectional and longitudinal studies have reported the association of GM damage and cognitive impairment in patients with MS.[46] Using double inversion recovery, Roosendaal et al reported that cortical lesions increased notably over 3 years, the number of cortical lesions was higher in patients with SPMS compared with RRMS, and these lesions were associated with cognitive impairment.[54] Mike et al have reported that cortical lesion number and volume correlated with EDSS and SDMT scores in a sample of 26 patients with MS.[55] These authors also reported that cortical lesion number correlated with CVLT-II scores. Additional evidence supporting an association between intracortical lesions and neuropsychological testing performance was provided by a study of 39 patients reported by Nelson et al.[56] GM atrophy and atrophy of specific structures such as the thalamus and hippocampus have also been linked to cognitive impairment in patients with MS.[57] Amato et al conducted a study of 41 patients with RRMS and 16 matched healthy controls to assess the relationship between volumetric MRI measures and neuropsychological performance.[58] The study showed that MS patients had significantly lower normalized cortical volumes compared with the control group, and there were significant correlations between normalized cortical volume and measures of verbal memory, verbal fluency, and attention/concentration of patients with cognitive impairment. Neuropsychological measures did not correlate with normalized cortical volume in patients who were cognitively preserved. In a cross-sectional analysis of 50 patients with MS, Benedict et al reported significant correlations between lower regional volume of the medial temporal lobe (hippocampus and amygdala) and deep GM (thalamus and caudate) and neuropsychological memory tests.[59] Deep GM volumes were most strongly predictive of measures of free recall or new learning. In a study of 86 patients with MS and 25 healthy controls, Batista et al reported that after controlling for neocortical volume, deep GM volumes significantly correlated with SDMT performance, with the strongest effects associated with the putamen and thalamus.[60]

Episodic memory impairment is frequent in patients with MS (up to 50%) and can be present early in the disease course (~25% of patients with CIS).[61,62] Memory encoding and retrieval have been correlated with hippocampal volume loss in MS, however the anatomical substratum of episodic memory impairment in the very early stages of MS is not known.[63] Brochet et al conducted a clinical study in the CIS patient population and an experimental study using the experimental autoimmune encephalomyelitis (EAE) model to better understand the underlying mechanism for the memory impairment in MS patients.[64] The clinical study included a cohort of 37 patients with CIS compared with healthy controls and also a group of MS patients with some cognitive impairment who served as positive controls. The groups differed with regard to disease duration, mean EDSS scores and MRI metrics. Cognitive assessment showed that 27% of the CIS patients had impaired verbal episodic memory (learning trials and long term recall) compared with 66% and

63% of the MS patients with impairment on these tests, respectively. Using DTI, analysis of the hippocampus showed a significant decrease of fractional anisotropy in the group of patients with CIS compared with healthy controls, and an even larger decrease in the MS patient population. There was also a significant increase in mean diffusivity in the CIS group, but no evidence of atrophy of the hippocampus, suggesting that the diffusivity and fractional anisotropy abnormalities appear before atrophy in the hippocampus. To better understand what was observed in the clinical study of patients with CIS, an EAE model was used for studying episodic memory. EAE mice showed an early hippocampal-dependent memory deficit, however the EAE mice did not show hippocampal atrophy as measured with T2-volumetry MRI. In vivo DTI of the hippocampus in EAE mice revealed selective microstructural modifications (differences in diffusivity and fractional anisotropy) in the molecular layer of the dentate gyrus that were not present in the other layers. Histological analysis confirmed the presence of a selective and early neurodegenerative process in the dentate gyrus; the loss of neurites was correlated with diffusivity and fractional anisotropy. These results suggest that DTI correlates with early microstructural changes in the hippocampus that could potentially be used as a biomarker of therapeutic response.[64]

Functional MRI usually measures what is defined as a physiological contrast; which is the change in the ratio between oxy- and deoxyhemoglobin within specific brain regions when these regions are involved in the performance of a specific task (for the purposes of the current discussion, a cognitive task).[65] In addition to measuring the activity within a specific brain region, it is possible to assess how the activity within a single region is synchronized with the activity in another region. This is usually defined as functional connectivity. How activity between different regions is modulated by the administration of a task or the complexity of a task is defined effective connectivity.

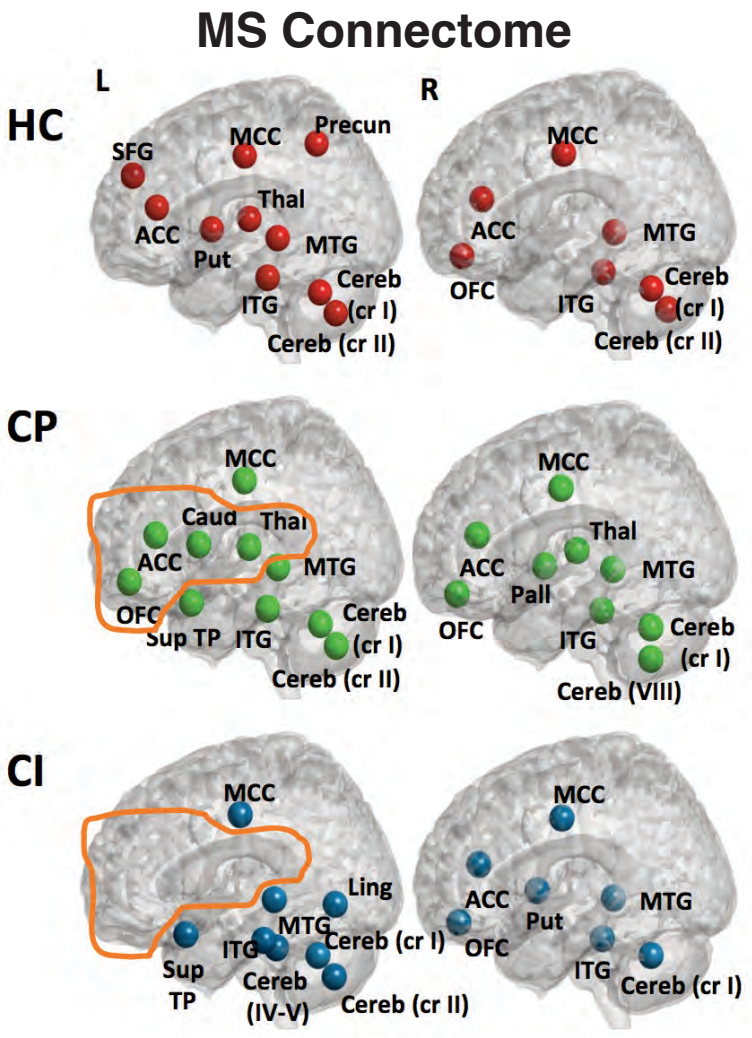
Evidence from studies using the active fMRI paradigm to assess the cognitive network of patients with MS demonstrates that in patients who are not cognitively impaired, there is an early abnormality within the cognitive network that can be detected even in patients with CIS, and this is characterized by increased and more bilateral recruitment of the network of interest.[66] These abnormalities are also present in patients with RRMS without cognitive impairment, and also later in patients with benign MS who are cognitively preserved.[67,68] Modification of an activity within cognitive networks is strongly modulated by the presence of structural damage, including lesions within the WM, extensive damage within the NAWM, and also extensive damage within the GM.[69,70]

In a multifocal disease such as MS, damage to a strategic part of the CNS might be more clinically relevant than the presence of widespread damage in different CNS compartments, and there are different strategies to better understand this. One approach is to combine measures of both functional and structural connectivity, such as by using diffusion tensor tractography. What has been shown by such an approach, at least in patients with RRMS (at the beginning of disease), is a relationship between damage within cognitively-related tracts such as the superior longitudinal fasciculus where there is decreased fractional anisotropy, and a more bilateral pattern of cortical recruitment.[71] The same applies later on in patients with benign MS where there is increased modification of connectivity between different cognitive regions within the brain hemispheres, modulated by the presence of damage only within cognitively related white matter tracts, such as the superior fronto-occipital fasciculus, uncinate fasciculus, cingulate cortex and fornix.[68] There are more examples of increased or a more bilateral pattern of cortical recruitment related to underlying structural damage in patients who are cognitively preserved. This has led to the hypothesis that what we can measure with these techniques is adaptive for these patients counteracting the presence of widespread structural damage; however there is also some evidence suggesting that sometimes what is

measured with fMRI is maladaptive and associated with poor cognitive outcome. For example, Penner et al showed that patients who had severe cognitive impairment had a poor or exhausted pattern of cortical recruitment within different cognitive networks compared with those MS patients with mild cognitive impairment.[72] There are other studies that have demonstrated these maladaptive cortical organizations—for example in a study of patients with PPMS and cognitive impairment, patients who are cognitively impaired had higher recruitment of posterior brain regions (within the cerebellum, related to worse cognitive performance).[73] In addition, Rocca et al consistently demonstrated that fatigue in patients with MS is associated with abnormal recruitment of a frontal thalamic network.[74]

The main issue when planning to apply an active fMRI task to patients with MS who might be cognitively impaired, is how much can you trust the results—and how much of the results might be influenced or biased by the capability of patients to do a particular task compared with healthy controls. A strategy to minimize such confounding factors is to assess connectivity within or between the main functionally relevant brain networks in the condition of the resting state. What has been shown with this approach is that even when we analyze functional connectivity at rest, there are early abnormalities of functional connectivity in patients with CIS who are not cognitively impaired. The abnormalities of functional connectivity seem to involve the majority of the resting state networks, including cognitively-related networks, sensory and visual networks compared to healthy controls or patients with RRMS.[75] In addition to these abnormalities within the different networks there are also diffuse abnormalities of communication among the different networks; with some increased cross talk between networks and others with decreased cross talk.[76] In patients with progressive MS and severe cognitive impairment, when the default mode network is analyzed, there is a reduction in functional connectivity. This reduction in functional connectivity in patients with progressive MS seems to affect the anterior mode of the network, notably regions within the frontal lobe and medial structures.[77]

Figure 3: Graph Analysis–Loss of Hubs in Patients with MS and Cognitive Impairment



HC: healthy controls; CP: cognitively preserved; CI: cognitive impairment. With permission of Maria A. Rocca, MD

The notion that cognitive impairment in patients with MS is related to functional abnormalities within the frontal lobe is supported by more recent studies using graph theory analysis. In a large cohort study of patients with MS, Rocca et al demonstrated that patients who are cognitively impaired show a loss of hubs in their left frontal lobe as compared with healthy controls **(Figure 3, previous page)**.[78]

When studying patients with pediatric MS, a completely different representation of brain cortical hubs has been found; specifically there seem to be more hubs located in the posterior brain regions and cerebellar regions, which is different than in adults patients with MS. Additional findings reflective of the differences in the pediatric MS brain compared with adults relate to the default mode network. In adults with MS, there is disruption of the frontal hub of the default mode network (DMN), whereas in pediatric MS functional disruption of the posterior node of the network was found.[79] These functional abnormalities tend to colocalize with the presence of structural abnormalities. In addition, the analysis of functional network connectivity showed just a few modifications with communication between the different networks.[80] These findings prompt consideration of whether this peculiar pattern of cortical organization in patients with pediatric MS might be protective, deferring development of disability, or if it is simply a maturational effect that is representative of widespread WM damage (not allowing appropriate maturation within the connections in the different networks). Longitudinal studies of pediatric patients with MS will help to better inform understanding of these findings.

Specific regions in the brain that are particularly interesting to this discussion are the hippocampus and the thalamus. In the hippocampus, there are abnormalities of both activation and of functional connectivity that follow the same paradigm discussed previously—patients that are cognitively preserved have higher recruitment, activity, and higher functional connectivity within the hippocampal network, while patients that are cognitively impaired have lower activity and connectivity.[81,82] In patients with MS, there is a disconnection between the hippocampus and the entire default mode network.[83] Hippocampal resting state functional connectivity is strongly influenced by the accumulation of lesions within the WM, and is strongly correlated with longer disease duration, and the severity of depression and disability.[83] Another structure of interest is the thalamus. Thalamic atrophy has been demonstrated in patients with MS from the beginning of the disease and has been proposed as a possible biomarker for cognitive impairment. In addition to atrophy, it has been consistently demonstrated that there is an early increase in thalamic functional connectivity in patients with MS, and this functional connectivity might be maladaptive, since it is related to poor cognitive performance.[84,85]

The general paradigm of functional organization in patients with MS appears to be that increased functional connectivity and activity within functionally relevant brain networks are present in those patients who are cognitively preserved, while patients with cognitive impairment have a progressive decrease of activity and functional connectivity. The exception being that of in the thalamic network where there is disinhibition of this network likely due to WM damage of tracts that connect the thalamus to cortical regions. However one must consider that at present the data regarding potential adaptive/maladaptive roles of increased or decreased functional connectivity in these brain regions are still controversial, and there are many theories concerning the role of functional organization in patients with MS.[86-88]

Meijer et al conducted a study to explore whether the DMN and the frontal parietal network (FPN) are changed in cognitively impaired patients with MS. Specifically, these investigators were interested in whether severe cognitive impairment in MS can be explained by disturbances in connectivity within the DMN and FPNs, between the DMN and FPN,

or DMN and FPN connectivity to the rest of the brain.[89] The study included 332 patients with MS (180 cognitively preserved, 87 cognitively impaired, and 65 with mild cognitive impairment) and 96 healthy controls. Compared with the other groups, patients with MS and cognitive impairment had more brain volume loss and a greater total T2 WM lesion load. Patients with cognitive impairment scored significantly worse on all cognitive domains assessed than cognitively preserved, and the most severely affected domains were information processing speed, working memory and executive function. For each of the regions of interest, connectivity matrices were based on Pearson correlation coefficients. Within and between network connectivity for the DMN and FPN were normal in the patients with cognitive impairment. Higher connectivity between both the DMN and FPN and the rest of the brain were significantly correlated with worse processing speed and working memory. Higher connectivity between the DMN and the rest of the brain was associated with poor verbal memory and executive function. Increased connectivity between the FPN and the rest of the brain was associated with poor attention. Predictors of worse cognitive function in patients with MS were found to be increased age, male sex, loss of deep GM volume, and increased relative connectivity with the rest of the brain.

It has been shown that patients with MS have an impaired functional reserve. MS patients have an inability to increase recruitment within a given network (particularly a cognitive network) during the increasing demand imposed by doing a cognitive task. It is not possible to measure such mechanisms by resting state analysis, but instead this can be assessed by using a cognitive task with increasing load of demand (fMRI paradigm with Go/No-go conditions or N-back task). Impaired functional reserve is present at the beginning of the disease in patients with CIS and it becomes prominent in patients with RRMS and SPMS.[90,91] Since optimization of this functional reserve might be a target for possible cognitive rehabilitation efforts, there is a need to use an active fMRI paradigm for monitoring such mechanisms.

Another strategy to define an adaptive or maladaptive role of cortical organization is to perform longitudinal studies with fMRI in patients with MS. Audoin et al showed that increased activity in the dorsolateral prefrontal cortex over a 1-year period in patients with early RRMS was associated with better performance of a cognitive task.[92] Conversely, Loitfelder et al showed that increased activity within the inferior parietal lobe over a 1-year period was associated with worse performance on the SDMT in patients with RRMS.[93] The function and specialization of different regions of the brain might explain these discrepant findings.

A few studies have applied fMRI to monitor drug effects. Cader et al reported that both the acute and chronic administration of rivastigmine can modulate recruitment of cognitive networks, but this did not appear to have a beneficial effect on cognitive performance.[94] There is a recent study showing that cannabis can result in a poor pattern of recruitment during a cognitive task (PASAT).[95]

Cortical reorganization is a common phenomenon in patients with MS independent of disease duration and clinical phenotype. There are variable patterns of cortical rewiring with the potential to limit the functional consequences of tissue damage that occur in MS patients. This suggests that clinical manifestations are likely to result from the balance between structural damage and cortical reorganization, rather than being a pure reflection of tissue disruption. Together with adaptive plasticity, maladaptive plasticity can also occur in the brain networks of patients with MS, which contributes to the accumulation of disability and cognitive impairment. Interventions that modify neuroplasticity can promote functional restoration by inducing adaptive changes or by predisposing functional systems to adaptive plasticity. An improved understanding of recovery mechanisms may contribute to guide the development of recovery-oriented strategies in MS.

Interventions for Cognition in MS

Faculty: Robert W. Motl, PhD

COGNITIVE REHABILITATION

Common cognitive impairments seen in patients with MS include deficits in new learning, memory and processing speed, and these deficits are the focus of much of the cognitive rehabilitation literature currently.[96] There has been a significant increase in the literature related to studies of cognitive rehabilitation for patients with MS over the last 8-10 years.[97]

The modified story memory technique is a strategy for memory rehabilitation that has been studied in patients with MS. This technique is a 10-session, computer-based cognitive rehabilitation program that teaches patients context and imagery to facilitate learning.[98] Chiaravalloti et al conducted a study with 86 participants with MS who had demonstrated objective impairment in new learning ability. The study was conducted with double-blinded conditions and patients were randomized to either the memory retraining or control groups. Neuropsychological performance (CVLT) was not different between the groups at baseline; however there was a significant improvement in participants' ability to learn words across trials of the CVLT in the treatment group vs. controls (improvement in CVLT slope, $P = 0.02$).[98] In addition, there was a difference in self-report of everyday life between the groups following the intervention (greater improvement associated with the modified story memory technique), as assessed by the Functional Assessment of Multiple Sclerosis (FAMS) General Contentment score and the Frontal Systems Behavior Scale (FrSBe) Total Score, Family Form.[98] Follow-up after modified story memory training showed that improvement in memory performance observed immediately following the intervention was maintained 6-months later.[99]

Techniques borrowed from cognitive psychology have also been applied to improve new learning in patients with MS. Stylistic memory enhancement (a treatment protocol) teaches persons with MS and their significant others how to apply generation effect, spacing effect, and testing effect techniques in daily life. The inclusion of significant others in this approach is particularly important since many of the adjustments are environmental modifications. This strategy is an 8-session treatment protocol, and preliminary questionnaire data from Chiaravalloti et al demonstrate improvement in FAMS general contentment scores, improvement in the Health Status Questionnaire general health scores, and improvement in prospective memory on the Perceived Deficits Questionnaire (PDQ) compared to baseline.[100]

Ernst et al have studied a cognitive rehabilitation program focused on autobiographical memory deficits in patients with MS.[101,102] In a pilot study with 10 patients who were taught to use mental visual imagery when evoking personal recollections, all patients showed improvement in autobiographical memory and self-reported positive effects in activities of daily living.[101] These investigators conducted a randomized controlled trial in 40 patients with MS and autobiographical memory and episodic future thinking impairment. Patients were randomized to either the experimental (mental visual imagery program), sham verbal program control or a stability group (no intervention). Autobiographical assessment scores showed significant improvement in autobiographical memory and executive functioning in the experimental group only.[102] Self-reported transfer of benefits to daily life was also reported for the rehabilitation group.

Processing speed and an individual's baseline processing speed ability play a substantial role in

their ability to benefit from memory retraining. It has been noted that persons with a processing speed impairment benefit much less from a memory intervention compared to those without such an impairment; therefore it is extremely important to address issues related to processing speed in patients with MS. Chiaravalloti et al have an ongoing randomized clinical trial with speed of processing training for patients with MS. This is a 10-session computerized, lap-top, manualized processing speed treatment program that has been used extensively in normal aging at the University of Alabama by Dr. Karlene Ball and has been associated with improvement in neuropsychological performance and performance of everyday activities.[103] There are 3 levels to the training: single discrimination, discrimination task with a peripheral target, and discrimination task with peripheral target embedded among distractors. Patients move through different levels based on individual performance. Assessments are made at baseline, one week post-treatment, and at 6 months post-treatment. Data from a pilot study with this speed of processing training approach in 18 patients with MS demonstrated significant improvement in processing speed from baseline to follow-up compared to a control group.[100] Training was also associated with significant improvement in time to completion of various tasks (Timed Independent Activities of Daily Living, TIADL) from baseline to follow-up and compared with controls.

Hancock et al recently published a study looking at a processing speed treatment and memory training for persons with MS that included the Posit Science InSight and Brain Twister visual n-back programs.[104] These programs were training for processing speed deficits and working memory deficits; patients completed training with 3 weeks of one program and then 3 weeks of the other. Following the 6-week training program, the authors reported a significant improvement on the PASAT compared with sham training (baseline to follow-up). Methodological limitations associated with this study include a lack of objective cognitive screening at baseline (therefore it is not clear that all patients had processing speed impairment) and there was high attrition over the course of the study.[104]

RehaCom is a cognitive rehabilitation protocol used extensively in Europe. RehaCom has over 20 modules, is available in 10 languages, and excellent results have been demonstrated with attention and executive functioning.[105] Mattioli et al conducted a study with RehaCom in 20 persons with MS who scored below established cut-off levels on the PASAT and Wisconsin Card Sorting Test.[106] Patients assigned to the treatment group underwent the RehaCom program for 12 weeks (1 hour session, 3 days a week) and the control group had no cognitive rehabilitation. Neuropsychological evaluation was conducted at baseline and after 3 months. After 3 months, patients in the rehabilitation program had significant improvement in tests of attention, information processing and executive functions; the median changes from baseline to 3 months were significantly different from the control group.[106] The authors followed this study with a 9 month post-treatment evaluation, and demonstrated stability in the treatment effects; significant improvement in processing speed, executive function, depression and quality of life endpoints were maintained over time.[107] Consistent results were published by Filippi et al who also demonstrated significant improvement in attention, information processing and executive functions in MS patients with the RehaCom program compared with controls.[108] Additional studies have demonstrated improved cognitive performance in patients with MS and RehaCom, including correlation of imaging findings (fMRI) with neuropsychological changes.[108-110] RehaCom was utilized in a 1-year study conducted at 10 MS centers in Italy. Specific intensive cognitive training was associated with significant benefits at 1 year, including on the PASAT, SDMT, and tests of visual and verbal memory compared with patients who engaged in aspecific psychological intervention.[111] In a follow-up study, these investigators demonstrated that the beneficial effects associated with RehaCom treatment in the first year persisted up to 2 years for the patients in the specific intervention group.[112]

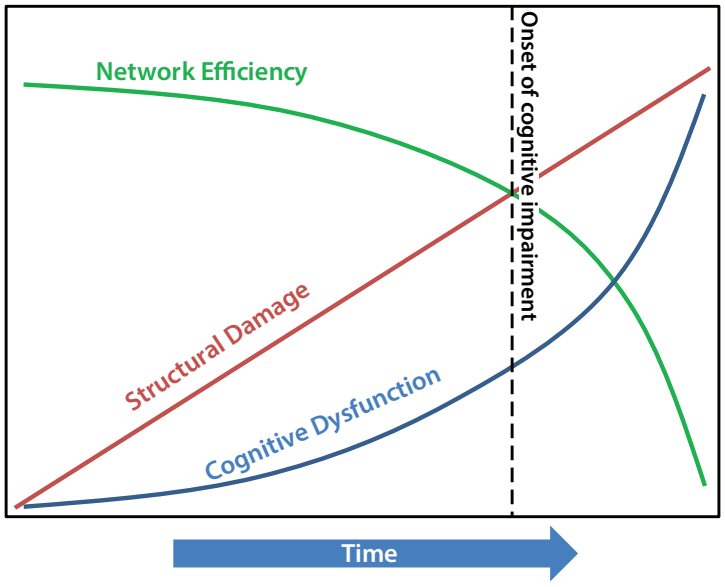
There is increasing interest in at-home-based cognitive rehabilitation programs for patients with MS. De Giglio et al recently reported results of a study with 24 patients with MS and cognitive impairment that were randomized to either a home-based computerized intervention or wait-list control group.[113] After 8 weeks of cognitive rehabilitation, there was significant improvement in the PASAT, SDMT, and *STROOP* test performance for the intervention group compared with wait-list controls.[113] These authors also reported increased functional connectivity in the cingulum, precuneus, and bilateral parietal cortex and lower functional connectivity in the cerebellum and left prefrontal cortex in the intervention group at follow-up compared with the wait-list group. Correlations were found between the changes in functional connectivity in these brain regions and improvement in cognitive performance.[113] [These results are in contrast to the report by Schoonheim et al in which patients with MS and cognitive impairment were reported to have high functional connectivity in the thalamus.[85]]

While the importance of cognitive rehabilitation cannot be overstated, it is important to note that a Cochrane Review published in 2014 reported low-level evidence for positive effects of neuropsychological rehabilitation in patients with MS.[114] The authors reported that the comparability of the 20 studies reviewed was limited due to heterogeneity of interventions and outcome measures, however the majority of studies did show some evidence of positive effects on cognitive endpoints.[114] An ever-growing body of evidence supports the benefits of cognitive rehabilitation for persons with MS and more randomized controlled trials are needed to support existing and new rehabilitation techniques. Approaches that can be utilized in a home environment are important, as travel to a clinic for multiple treatment sessions can be challenging for the MS patient population. Questions remain as to which cognitive rehabilitation interventions work best for specific patients and what point in the disease process is optimal to implement these interventions. 'Dosage' is an important consideration for cognitive rehabilitation strategies—what is optimal and at what point do you lose benefit? Studies that include greater numbers of patients with progressive MS are needed to identify cognitive rehabilitation strategies that specifically support this patient population.

COGNITIVE REHABILITATION—IMAGING

Cognitive decline in MS is hypothesized to be the result of network collapse as illustrated in Figure 4.[115] Structural damage in the brain increases over time with MS, and as whole network efficiency decreases with increasing underlying structural damage, ultimately a critical threshold is exceeded, beyond which the network is unable to function normally and cognitive impairment ensues.

Figure 4: Network Collapse: The Evolution of Cognitive Decline (adapted from[115])



The potential for inducing structural changes in the brains of healthy people was first reported by Draganski et al in 2004, where they described significant increases in the grey matter volume of brain areas responsible for complex visual movements induced by juggling training.[116] Another study replicated these findings showing changes in the grey matter induced by juggling training and also noted changes in the white matter as shown with fractional anisotropy.[117] Cognitive training was also demonstrated to induce functional or adaptive changes in the brains of healthy persons. Using fMRI, several studies showed that specific working memory training was associated with increased activity in the parietal cortex and the dorsolateral prefrontal cortex.[118-120] In 2006, Penner et al published a study of cognitive training and fMRI in patients with MS.[121] Activation patterns before and after cognitive training showed an increase in activation of the same areas noted prior to cognitive training and in additional areas activated after the training as well. This change was considered an adaptive change because the change was related to the specific task that the patients performed.[121] This finding was replicated by other investigators including Sastre-Garriga et al who showed that training with a cognitive rehabilitation program was associated with increased brain activity in the cerebellum of patients with MS and cognitive impairment compared with healthy subjects using fMRI.[122] This result was considered an adaptive change as the tasks applied were specifically associated with the cerebellum. As noted previously, the modified story memory technique has been shown to significantly improve new learning and memory in patients with MS. Using fMRI, Chiaravalloti et al demonstrated improvement in cognitive task performance and increased activation in the frontal, parietal, precuneus, and parahippocampal regions with the modified story memory technique, and these activated regions were specific to the tasks performed.[123] Recently, Huiskamp et al published results of a study using fMRI during a working memory task after training with the modified story memory technique in patients with MS.[124] Compared to the control group, treatment with the modified story memory technique was associated with increased activation in brain areas related to the task performed, including the inferior parietal lobe, the dorsolateral prefrontal cortex, and the supplementary motor area. However, the behavioral data in this study did not show a significant improvement in task performance associated with treatment, which complicates the interpretation of the functional imaging results.[124] Parisi et al investigated the effects of a 12-week cognitive rehabilitation program for MS patients on neuropsychological performance and resting state functional connectivity.[125] At 3 months following completion of the rehabilitation program, improvements in neuropsychological scores were significantly correlated with resting state functional connectivity in cognitive-related networks and the resting state functional connectivity of the anterior cingulum. Resting state functional connectivity changes in the default mode network were found to predict cognitive performance.[125]

Cognitive rehabilitation is useful for all patients with MS regardless of disease course and level of cognitive impairment. It is never too late to introduce cognitive rehabilitation, even in patients with severe impairment, however rehabilitation is recommended early in the disease course so that benefits can be realized from the existing functional networks. It will be important to increase our knowledge on what are considered adaptive and maladaptive changes when interpreting functional imaging findings. Areas of increased activation associated with a given task may not necessarily mean a beneficial response.

EXERCISE AND COGNITION IN MS

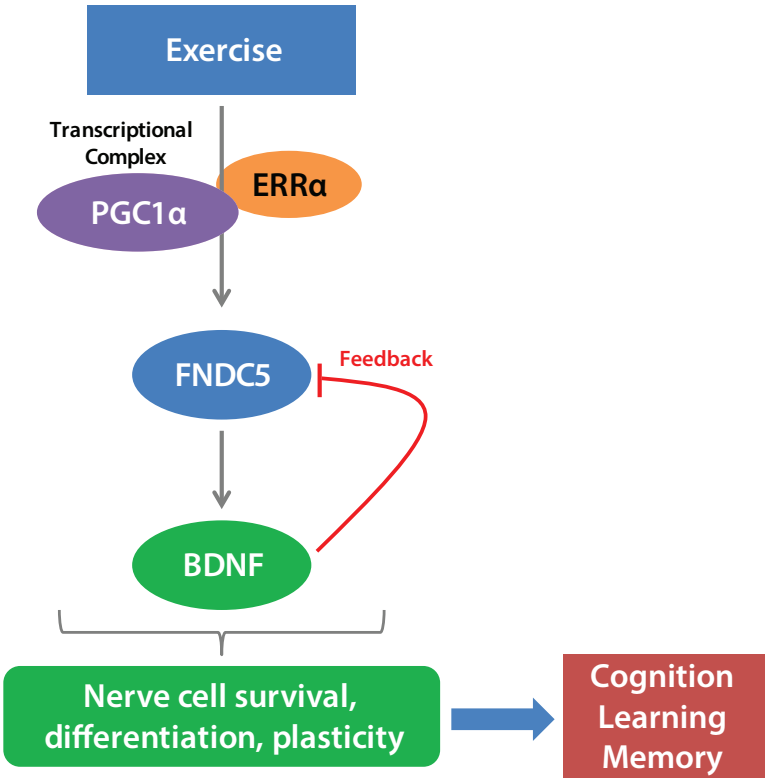
The foundation for interest in exercise and cognition derives from studies of exercise in older adults. In a seminal study published by Spirduso and Clifford, the investigators compared young and old racquet sportsmen, runners, and sedentary persons in their ability to do a simple reaction time task.[126] The key findings from this cross-sectional study were that older sedentary adults had slower reaction

times than active older adults, the reaction time of older active individuals was similar to sedentary younger adults, and older racquet sportsmen had faster reaction times than older runners.[126] The primary implication from this study was that aerobic activity may slow the decline of mental processing speed with aging, but not as effectively as racquet sports (perhaps due to the rapid hand-eye coordination involved in racquet sports—in a way continuing to train mental processing). In a landmark study, Kramer et al studied a group of 124 previously sedentary older adults (60-75 years old) who were randomized to either walking (aerobic exercise) or stretching and toning (anaerobic exercise) for 6 months and evaluated their performance of cognitive tasks.[127] Those individuals who received aerobic training demonstrated improvements (reduced reaction time) in performance of tasks requiring executive control compared with individuals who completed anaerobic exercise training.[127] In a meta-analysis published in 2003, Colcombe and Kramer reviewed randomized controlled trials that examined the effect of exercise training on cognitive functioning.[128] The authors reported that exercise training was associated with a significant improvement of approximately a half standard deviation across all domains of cognitive functioning, and this effect was larger than the control condition in these studies.[128] In addition, this analysis showed that aerobic exercise combined with resistance training was associated with larger effects on cognitive function than aerobic exercise alone. Greater separation was noted between controls and aerobic exercise with the more demanding cognitive tasks, i.e., those that involve brain activation involving the frontal/prefrontal cortex.[128] It was hypothesized that the beneficial effects observed with exercise and cognitive functioning were related to a slowing of brain tissue loss and/or neurogenesis, as MRI studies have shown regions of the brain that are preserved with cardiovascular fitness, including the frontal/prefrontal cortex, parietal cortex, and temporal cortex.[129,130] Such benefits of aerobic exercise are not thought be a result of increased brain blood flow, as Musch et al have demonstrated in foxhounds that while there might be a slight increase in brain blood flow during acute exercise, chronic exercise training does not affect resting or exercise brain blood flow.[131] Studies in animal models have demonstrated that brain-derived neurotrophic factor (BDNF) and other growth factors are increased with exercise.[132] Wrann et al have shown that the underlying mechanism between aerobic exercise and brain growth factors is via the production of the protein FNDC5 in muscles with contraction, which then increases the expression of BDNF in the hippocampus **(Figure 5, next page)**.[133]

There have been some conflicting reports of exercise and cognition in patients with MS. A 6-month study by Oken et al compared weekly yoga class with home practice, weekly exercise class using a stationary bicycle with home practice, or a wait-list group on a battery of cognitive tasks and showed no relative improvement of cognitive function with either of the exercise groups.[134] In contrast, Briken et al reported that an 8-10 week exercise training program produced benefits on fitness and several domains of cognitive function in patients with progressive MS.[135] As noted by Motl et al, the body of evidence related to exercise training and improvement in cognitive function in older adults provides compelling background to research the potential benefits of exercise on cognitive functioning in patients with MS.[136]

Sandroff et al conducted a cross-sectional study to examine the associations between aerobic capacity, muscle strength, and cognitive function in persons with mild, moderate and severe MS disability.[137] In this study of 62 persons with MS, aerobic capacity was used as a proxy for exercise training. Aerobic fitness and muscle strength were strongly correlated with SDMT performance; this relationship was primarily apparent in those individuals with MS and mild disease.[137] A study of 24 persons with RRMS compared the acute effects of moderate intensity treadmill walking, moderate intensity cycle ergometry, guided yoga and quiet rest on

Figure 5: Model of the Hippocampal PGC-1α/ FNDC5/BDNF Pathway in Exercise (adapted)[133]



PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ERR α: estrogen-related receptor alpha; FNDC5: fibronectin type III domain containing protein; BDNF: brain-derived neurotrophic factor

performance of a Modified-Flanker task as a measure of executive control.[138] Treadmill walking was shown to have the largest effect on executive control in this patient group.[138] A follow-up study looked at the intensity of acute treadmill walking in this model and demonstrated no differences between light, moderate and vigorous treadmill walking intensity for acute changes on the performance of the Modified Flanker task.[139] Sandroff et al extended these findings to a pilot study evaluating the effects of a 12-week exercise training intervention on cognitive processing speed and executive function in a group of ambulatory persons with MS.[140] In this study, 10 patients with MS and EDSS scores ≤ 4.0 who were relapse-free for 30 days were randomized either to a 12-week progressive treadmill walking exercise training program or a wait list. The primary outcome measures were cognitive processing speed (SDMT, Modified Flanker Task), executive function (Delis-Kaplan Executive Function System [DKEFS] Sorting test, and Modified Flanker Task), and cardiorespiratory fitness measured by a graded exercise test; these assessments were conducted at baseline and following the 12-week intervention.[140] Compared with the wait-list control, the exercise program was associated with large effects on SDMT and VO_2 peak (Cohen's d = 0.95 and 1.08, respectively). Minimal changes were observed with the DKEFS and Modified Flanker Test. The change in VO_2 peak was significantly correlated with change in SDMT, providing initial proof-of-concept support for progressive treadmill walking exercise training as a potential means for improving cognitive processing speed and cardiorespiratory fitness in persons with MS. Preliminary resting state fMRI analysis has shown large exercise-related increases in thalamocortical resting state functional connectivity, and these changes were associated with changes in SDMT and cardiorespiratory fitness.[140]

Motl et al conducted a study examining the association between cardiorespiratory fitness and volumes of deep grey matter structures associated with cognitive and motor functions in patients with MS.[141] MRI and aerobic fitness data from 35 patients with MS showed that individuals with higher cardiorespiratory fitness had larger scaled volumes of the hippocampus and basal ganglia structures.[141] Further study with a more restrictive

model has shown that moderate to vigorous physical activity is significantly associated with volume of the hippocampus, thalamus, caudate, putamen, pallidum, normal white and grey matter volumes in patients with MS.[142] Leavitt et al recently published a case study looking at the effects of aerobic exercise on learning and memory and hippocampal volume and functional connectivity in two memory-impaired patients with MS.[143] Aerobic exercise was associated with an increase in hippocampal volume, increase in memory, and an increase in hippocampal resting state functional connectivity, changes that were not apparent with non-aerobic exercise. There is great interest in the potential benefits associated with combining exercise training and cognitive rehabilitation in patients with MS.[144]

MEDICATION & COGNITION IN MS

Studies of pharmacological approaches to the treatment of cognitive impairment in patients with MS can be placed in two categories, namely trials with disease modifying therapies (DMTs) and studies with symptomatic therapies. One of the challenges in conducting studies with pharmacological agents for cognition in MS is that the change in cognition over time at the group level is very slow. Strober et al conducted a longitudinal study of 22 patients with MS comparing neuropsychological performance at study initiation and at 18 year follow-up.[145] Over the 18 years of study, measures of information processing speed, simple and complex auditory attention, episodic learning and memory, and visual construction declined. Eighteen percent of those who were cognitively preserved at baseline were cognitively impaired at follow-up, highlighting the slow change over time. Only the SDMT demonstrated a group by time interaction in this study.[145]

Studies of cognition with DMTs in patients with MS have shown modest beneficial effects. Neuropsychological function was assessed longitudinally in 30 individuals with MS who participated in the pivotal trial of interferon beta-1b (IFNβ-1b).[146] Of the neuropsychological endpoints evaluated, significant improvement was observed only in the Wechsler Memory Scale Visual Reproduction-Delayed Recall between years 2 and 4 of the trial for those patients treated with high-dose IFNβ-1b.[146] Treatment with low dose IFNβ-1b did not have a beneficial effect on visual memory. The effects of treatment with IFNβ-1a (30 μg IM, weekly) on neuropsychological performance were reported by Fischer et al.[147] In this study, a comprehensive neuropsychological battery (45 tests) was given once at baseline and at 24 months; additional measures were collected every 6 months. Controlling for baseline covariates, there were beneficial effects associated with IFNβ-1a treatment on information processing and learning/memory.[147] In a 24-month randomized, placebo-controlled trial with glatiramer acetate in patients with RRMS, neuropsychological assessments (sustained attention, perceptual processing, verbal and visuospatial memory, and semantic retrieval) were conducted at baseline, then at 12 and 24 months after randomization.[148] Mean test scores were not different between the treatment groups at the end of 2 years of treatment.[148] A potential confounding factor with this study was the lack of initial cognitive impairment at baseline in both treatment groups.

Using a voxel-based morphometry and volumetry approach, MacKenzie-Graham et al have evaluated the association between localized grey matter atrophy and clinical disability in patients with RRMS.[149] In a group of 133 female patients with MS, they have demonstrated that worse performance on the PASAT correlated with volume loss in the primary auditory cortex and medial parietal cortex.[149] This approach was also applied in an exploratory analysis of the recently published estriol treatment study.[150] In the phase 2 study, Voshkuhl et al showed that treatment with glatiramer acetate plus estriol was associated with a 32% reduction in relapses at 24 months and a significant reduction in gadolinium enhancing lesions compared with glatiramer acetate plus placebo.[150] In addition, this study showed that higher estriol levels correlated with improved PASAT

scores.[150] Further, these authors demonstrated grey matter sparing in the estriol plus glatiramer acetate group, and a strong correlation between PASAT improvement and grey matter sparing ($P = 0.032$).[150] MacKenzie-Graham et al have applied voxelwise methods to these changes in grey matter observed in this study.[151] By investigating the longitudinal changes in grey matter associated with changes in the PASAT in the estriol trial combined with the longitudinal grey matter sparing, clinically eloquent areas were identified that were PASAT-associated grey matter spared by estriol.[151] These specific PASAT-associated regions overlap with Brodmann Areas 9 and 32, regions associated with the anterior attention system and implicated in problem solving. The authors conclude that this approach may be applicable to investigating other disabilities in MS and the treatment effects of disease modifying therapies in the MS patient population.

The MS Functional Composite (MSFC) was incorporated in the placebo-controlled AFFIRM study of natalizumab in patients with RRMS. Review of individual component scores of the MSFC from this trial showed that treatment with natalizumab over 2 years was associated with significant improvement on the PASAT relative to placebo.[152] While collectively these studies with DMTs have shown some promising results with cognitive outcomes in patients with RRMS, it may be that the short duration of the trials precludes realization a sizable change in cognitive endpoints.

Clinical trials of symptomatic treatments for cognitive impairment in patients with MS have largely produced negative results (summarized in **Table 5, next page**). The lack of available effective pharmacological approaches reinforces the importance of utilizing cognitive rehabilitation and/or exercise in order to improve cognitive functioning for patients with MS.

An estimated 40% of patients with MS have used cannabis at some point, such as for symptom management of pain or spasticity.[160] Cannabis is derived from the plant Cannabis Sativa, which contains over 60 cannabinoids. The most abundant of these is delta-9-tetrahydracannabinol (THC), which is psychoactive. The second most common cannabinoid is cannabidiol, which is lacking psychoactive properties. A few studies (with modest sample sizes) have evaluated the effects of cannabis on cognition in persons with MS. A small, 8-week, randomized, double-blind, placebo-controlled, parallel group, crossover trial evaluated the effect of cannabinoid treatment (with pharmaceutically manufactured, Sativex) in 17 cannabis-naïve patients with MS on several endpoints including the MSFC.[161] There were no differences between the post-placebo and post-cannabinoid groups on the MSFC, including the PASAT in this study. Ghaffar and Feinstein evaluated performance on the SDMT in a group of 10 subjects with MS who were current cannabis users compared with 40 demographically and disease-matched patients who did not use cannabis.[162] These authors reported statistically significantly slower mean performance time on the SDMT for cannabis users compared with matched controls.[162] A cross-sectional study by Honarmand et al conducted neuropsychological assessment in two groups of patients with MS; cannabis users and nonusers.[163] This study showed that patients with MS who were cannabis users performed significantly worse than nonusers on measures of information processing speed, working memory, executive function, and visuospatial perception. There was a significant difference between groups in global cognitive impairment (64% vs 32%, $P = 0.024$ for cannabis users and nonusers, respectively).[163] Pavisian et al conducted a study to determine the functional and structural neuroimaging correlates associated with cognitive dysfunction-related to cannabis use in persons with MS.[164] These authors reported that the cannabis group performed significantly more poorly during the 2-second PASAT and 10/36 spatial recall test compared with nonusers. In addition, cannabis users had a more diffuse pattern of cerebral activation during performance of N-back trials. Cannabis users also made more errors on a 2-back task, during which they displayed increased

Table 5: Symptomatic Treatments Evaluated for Cognition in Patients with MS

Treatment	Study	Outcome
Amantadine	Geisler et al, 1996[153] • 45 patients with MS and severe fatigue • 6-week parallel treatment design (amantadine, pemoline or placebo)	No significant differences between treatment groups on tests of working memory, attention, mental flexibility, verbal memory and learning, visual memory and motor speed
L-amphetamine	Benedict et al, 2008[154] • 19 patients with MS and 1 SD below norms on CVLT or SDMT, PASAT • Counterbalanced within-subjects design • Single dose administration of placebo, 15 mg, 30 mg, or 45 mg of l-amphetamine	Test performance improved with the highest dose of l-amphetamine, with the largest effects on the SDMT
Long-acting amphetamine (MAS-XR)	Morrow et al, 2015[155] • 62 patients with MS and processing speed impairment • Double-blind, placebo controlled trial • Single dose of 5 mg MAS-XR, 10 mg MAS-XR or placebo	10mg dose of MAS-XR showed improvement on SDMT, but not PASAT relative to placebo
Memantine	Peyro Saint Paul et al, 2016 [156] • 93 patients with RRMS and impaired verbal memory • Double-blind, placebo controlled, parallel group, randomized 52-week trial • Treatment with memantine (20 mg/day) or placebo	No differences between memantine and placebo on PASAT or SDMT
Rivastigmine	Shaygannejad V et al, 2008[157] • 60 patients with MS and cognitive impairment • Single center double-blind, placebo controlled randomized trial • 12 week treatment with rivastigmine or placebo	No differences in change scores between rivastigmine and placebo groups on the Wechsler Memory Scale after 12 weeks of treatment
Donepezil	Krupp et al, 2004[158] • 69 patients with MS and cognitive impairment • Single center, double-blind, placebo controlled trial • 24 week treatment with donepezil (10 mg daily) or placebo	Significant improvement on verbal memory (Selective Reminding Test) with donepezil vs. placebo at 24 weeks
Donepezil	Krupp et al, 2011[159] • 120 patients with MS and memory impairment • Multicenter, double-blind, placebo controlled trial • 24 week treatment with donepezil (10 mg daily) or placebo	No difference between placebo and donepezil treatment groups at 24 weeks on the Selective Reminding Test

activation relative to nonusers in parietal and anterior cingulate regions implicated in working memory.[164] Interestingly, in this study when patients performed the SDMT, thalamic activation was present in the cannabis naïve group, but lacking in those individuals who were cannabis users.[164] Collectively, these studies suggest that the potentially deleterious cognitive effects of cannabis should be weighed against benefits in other areas such as pain, spasticity, etc. for persons with MS.

COMPENSATORY STRATEGIES

Numerous compensatory strategies can be utilized to support cognitive challenges in persons with MS (Table 6).[165]

Table 6: Compensatory Cognitive Rehabilitation Strategies for People with MS (adapted)[165]

Challenge	Compensatory Strategy
Attention/concentration	• Minimize distractions: reduce clutter; work in a quiet area (low traffic, low noise) • Reduce interruptions: establish 'ground rules' with family and friends; let answering machine or voice mail pick up phone calls; use timers
Memory	• Notepads, planners, calendars • Voice recorders • Personal alarms • Memory buddy/partner • Colored baskets for specific items; always to be found in the same place • Locating devices for parked cars
Word retrieval	• Describe the item • Substitute one word for another • Free associate words • Use gestures
Visuoperceptual skills	• Finger or index card when reading • Large print books • Books on tape • Use brightly colored markers to mark left and right margins on a page • Highlight numbers that are frequently used in the phone book
Speed of information processing	• Ask others to slow down when they speak • Rephrase what others say • Repetition of information • Use voice recorders—go back and review information several times
Executive functions	• Make lists, and rank in order of priority • Write things down and make sure steps or ideas are in proper order • Take a moment to organize thoughts before responding

Cognitive Changes in Pediatric MS

Faculty: Christine Till, PhD, C.Psych

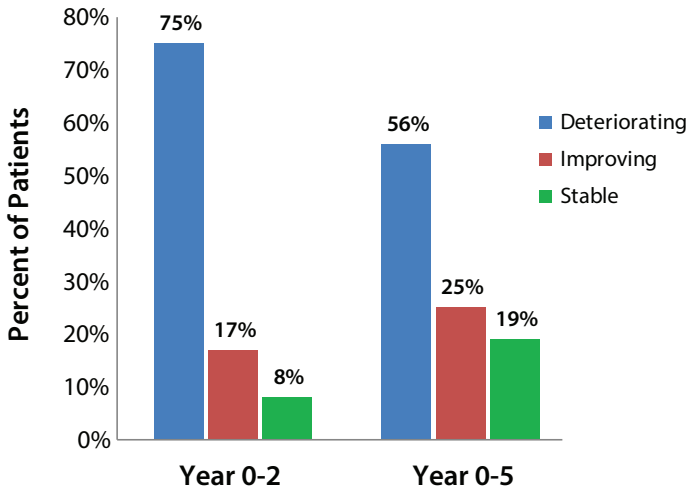
Children and adolescents with disease onset prior to the age of 18 years are considered to have pediatric onset MS (POMS). In comparison with the large body of evidence related to cognition in adults with MS, there is limited information on cognition in the pediatric MS population. In the past, research related to cognition in POMS was challenging due to the relatively small patient population, the absence of adequate control groups, and the narrow scope of neuropsychological assessments. However over the last decade, growing attention and awareness among clinicians and researchers has been directed toward this patient population. A few international groups have begun to conduct more rigorous and systematic research into this field to better assess the prevalence, neuropsychological profile, and the functional impact of cognitive changes in POMS.

Myelination of specific brain regions coincides with the development of specific cognitive functions including reading, vocabulary, linguistic skills, and executive decision making.[166] Myelination is well associated with normal cognitive development, IQ, reading skills and working memory.

Therefore, there may be a special vulnerability in patients with POMS, since the disease occurs during key periods of age-expected brain growth—a period of active primary myelination and maturation of neural networks. During the key formative years in the scholastic career of youth, inflammation in this form of the disease is very active, manifesting in clinical relapses and gadolinium enhancing MRI lesions (with greater frequency than in adults with MS). Brain plasticity and repair mechanisms in young patients may potentially help to mitigate disease-related pathologic changes, although long-term, longitudinal studies are needed to investigate this possibility.[167] It is important to note that the consequences of MS in a developing brain and early cognitive dysfunction can be evaluated only in a pediatric population and cannot be extrapolated from studies in adults with MS.

As reviewed by Amato et al, recent studies have consistently documented cognitive impairment in ~30% of patients with POMS, with the major areas of impairment including complex attention, verbal and visual memory, executive function, visuomotor integration, and in some cases aspects of linguistic skills.[168-172] The largest POMS sample studied to date was reported by Julian et al, which included 187 youth with RRMS and 44 with CIS.[172] The sample had short duration of MS (mean 1.9 years) and low impairment levels (median EDSS 1.5); 35% and 18% met the criteria for cognitive impairment in patients with RRMS and CIS, respectively.[172] Independent predictors of cognitive impairment were diagnosis of MS (vs. CIS), and overall neurological disability. The domains most frequently compromised in this POMS cohort were fine motor coordination (54%), visuomotor integration (50%), and information processing speed (35%).[172] Study of cognitively-related challenges in POMS has been extended to include social cognition and theory of mind. Theory of mind relates to how individuals interpret mental states of other persons and how such states are used to explain and predict the actions of others. Based on a study of 28 patients with POMS and 32 healthy controls, Charvet et al reported that patients with POMS had poorer performance on measures of theory of mind compared with healthy controls, including reduced facial recognition of affective state and reduced ability to identify beliefs and knowledge of others.[173] Poor theory of mind performance was not associated with demographic or clinical features; however it was associated with impaired performance on the SDMT.[173] Such results suggest that there may be challenges with social interactions in the future for these children so affected.

Figure 6: Longitudinal Changes in Individual Cognitive Performance over 5 Years in Youth with MS.[176]



Using an extensive neuropsychological test battery, a Canadian study provided longitudinal data over a 1-year period in children and adolescents with MS.[174] The study also included an age-matched group of healthy controls. At baseline, the prevalence of cognitive impairment in the POMS group was 29%.[174] Group performance at 1 year of follow-up showed that the healthy control group improved on all neuropsychological tests, whereas the POMS group improved only on 4 tests, a reflection of lack of expected age-related gains. Assessment of individual performance showed that 25% of the MS population declined on ≥3 neuropsychological assessments after 1 year, compared with 3.8% of the healthy control group.[174] The tests most responsive to decline were attention and information processing speed, visuomotor integration, visual memory, calculation, verbal fluency, and spelling ability. Deterioration in neuropsychological performance was associated with increased duration of MS and increased lesion volume on MRI.[174] Italian investigators have followed a cohort of patients with POMS and compared them with a control group from baseline through two and five years of follow-up.[170,175,176] At baseline, there were 63 patients, with a mean age of 15.3 years and low disability level (mean EDSS 1.5). An extensive neuropsychological battery was utilized (average duration of 2 hours) that included tests of IQ, memory, attention, executive functioning, and language. Psychosocial assessments evaluated symptoms of depression, fatigue, and performance of daily living activities. At baseline, the prevalence of cognitive impairment was 31%, and the primary domains involved were visual-spatial memory (56%), verbal memory (53%), information processing speed and attention shift (29-50%), abstract reasoning (41%), and expressive and receptive language (28-39%).[170] Eight percent of the POMS cohort had an IQ in the range of mild or moderate mental insufficiency, and these were patients with MS onset before age 10. In multivariate analysis, younger age at disease onset significantly predicted lower IQ score.[170] At 5 years, 48 patients of the original cohort were reassessed (15% dropout rate); the mean age of the sample was 19.7 years, all had RRMS, and the mean EDSS at this follow-up was 2.0.[176] After 5 years, there was deterioration in cognitive performance in 56% of patients, 19% were stable and 25% showed improvement on the cognitive assessments **(Figure 6)**.[176]

Functions more prone to deterioration at 5 years were visual spatial learning, verbal fluency and expressive language. Psychosocial interview data were available for 30 patients at the 5-year follow-up, and 83% of these patients were classified as having cognitive impairment. According to parental interviews, MS was having a negative impact on school activities (33%), negative impact on hobbies and sport activities (53%), and negatively affected family and social relationships (37%).[176]

Charvet et al reported results of a 1.6 year longitudinal (non-controlled) study of cognitive function in pediatric MS, with different results.

The study sample included 62 patients with MS and 5 with CIS, and 37% had cognitive impairment at baseline. After 1.6 years, most patients remained stable, 13% showed deterioration on cognitive testing and 20% improved on ≥ 2 tasks.[177]

Hosseini et al used growth curve modeling to assess longitudinal trajectories on the Trail Making Test-Part B (TMT-B) and the SDMT and to evaluate how age at disease onset, IQ, and social status may moderate the rate of cognitive change.[178] This analysis demonstrated that younger age at MS onset was significantly associated with cognitive decline on both the SDMT ($P = 0.005$) and TMT-B ($P = 0.001$), but there was no protective role of baseline IQ and parental social status (proxies of cognitive reserve).[178]

Pasto et al conducted a study to assess the potential impact of cognitive reserve on cognition in a cohort of POMS patients.[179] At baseline, cognitive impairment was detected in 29% of POMS patients and in 3.5% of healthy controls. Analysis after 4.7 years of follow-up indicated that higher baseline cognitive reserve (IQ) predicted stable/improving cognitive performance only in those patients who were cognitively preserved at baseline.[179] This result highlights the importance of early diagnosis, assessment and intervention for cognitive dysfunction in the MS patient population.

There are challenges associated with neuropsychological assessment for patients with POMS, including differences in developmental trajectories and the pattern of cognitive dysfunction that may be related to patient age and/or age at disease onset. Variable tools have been used in clinical studies, and there is a lack of robust psychometric and normative data for the pediatric population for most of the tests. A Brief Neuropsychological Battery has been developed for children with MS (BNBC).[180] The battery takes ~30 minutes and includes the vocabulary test from the WISC-R, SDMT, TMT-A and TMT-B, and selective reminding test (SRT-CLTR). Portaccio et al have used the BNBC to assess cognitive function in a sample of 61 patients with MS and 58 matched healthy controls. The authors reported that the BNBC had a sensitivity of 96% and specificity of 76% in predicting cognitive impairment in the pediatric MS population.[180] Another suggested battery has been recommended for use in POMS that incorporates SDMT, TMT-A and TMT-B, SRT, Beery VMI, and DKEFS Fluencies as core tests. This battery is estimated to take ~45 minutes for completion, but has not been implemented in published clinical trials to date.[181] Charvet et al have evaluated the utility of the SDMT as a tool for identifying POMS patients at risk for cognitive impairment.[182] Their study sample included 70 patients with POMS, 40 youth with other pediatric neurological diagnoses, and 32 healthy controls. The SDMT had a sensitivity of 77% and specificity of 81% for detecting neuropsychological impairment, and the authors concluded that this may be an effective brief screen for cognitive impairment in POMS, and one that could be useful as a cognitive assessment into adulthood as well. Akbar et al evaluated the maturational trajectory of SDMT performance in a combined cohort of Canadian and Italian patients with POMS.[183] In this sample of 82 patients, increasing age was associated with greater linear increase in SDMT performance through the end of adolescence. These investigators noted that by early adulthood, performance on the SDMT appears to plateau and gradually decline, suggesting that a peak level of performance is attained followed by subsequent decline.[183] This declining performance may reflect the accumulation of lesion volume and reduction in brain volume that negatively impact processing speed ability. This study also showed that younger age at MS onset negatively impacts maturational performance on the SDMT.[183]

Using a semi-structured psychiatric interview, Goretti et al have assessed psychosocial issues in an Italian cohort of children and adolescents with POMS.[184] In this sample of 56 patients, 30% were reported to have a mood disorder, including 15% with major depression, 5% with depression and anxiety, 5% with panic disorders, and 5% with

bipolar disorder.[184] More recently, psychiatric evaluation and neuropsychological assessment were conducted in a group of 45 patients with POMS.[185] Overall, 56% of the sample had psychiatric diagnoses, and most participants met the criteria for ≥ 2 diagnoses. The most frequently reported psychiatric disorders were anxiety disorders (48%), mood disorders (44%), and attention deficit hyperactivity disorder (48%).[185] Interestingly, those diagnosed with anxiety or mood disorders had the highest frequency of cognitive impairment (significantly higher than compared with those with other psychiatric diagnoses).[185] It is difficult to disentangle the relationship between cognitive impairment and mood disorders in terms of potential cause and effect.

NEUROIMAGING AND PEDIATRIC ONSET MS

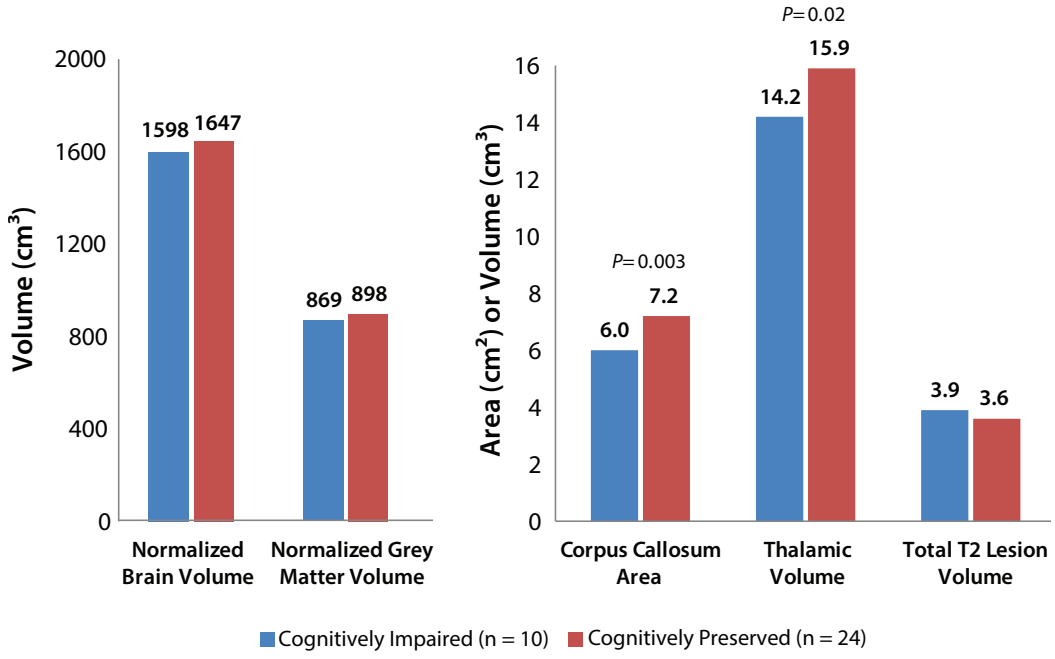
When comparing POMS with adult onset MS, disease activity appears to be higher in the POMS group. As shown by Waubant et al, when controlling for disease duration, large T2-bright foci, gadolinium-enhancing lesions, and T2-bright foci in the cerebellum, brainstem, corpus callosum, infratentorial and juxtacortical regions are present in a significantly higher proportion of patients with POMS relative to adults with MS.[186] A recent 3-year longitudinal study examined cortical pathology in both pediatric and adult-onset MS.[187] This study demonstrated that grey matter atrophy begins early (including in the pediatric population), and the rate of decline in grey matter fraction is similar between children and adults. Despite the same rate of grey matter atrophy, the time to develop disability has been shown to be longer in POMS.[188] This paradox of increased disease activity yet longer time to develop disability associated with POMS prompts consideration of whether there are protective factors to offset the risk for cognitive impairment in this younger patient population—and whether there may be greater potential for functional reorganization of brain networks.

A longitudinal study was conducted to quantify white matter, grey matter and deep grey matter structure volumes in patients with POMS.[189] This study included 38 children with MS and 33 age- and sex-matched controls; in addition, normative data from the NIH Pediatric Database were used for normalization and computing Z-scores. Results from this study showed that POMS is associated with failure of age expected brain growth, particularly in grey matter. Significant differences between the groups included normalized brain volume, normalized grey matter volume, and a particular vulnerability was thalamic volume (normalized for head size).[189]

To better understand the relationship between the cognitive profile of children with MS and MRI metrics, Till et al studied global metrics such as normalized brain volume, normalized grey matter volume, and T1/T2 lesion volumes; in addition, brain regions that were considered to be sensitive to mapping cognitive outcomes, including corpus callosum area, thalamic volume, hippocampal volume and the cerebellum were evaluated.[190] In this MS sample, 30% met criteria for cognitive impairment, with attention/processing speed, visuomotor integration, and cognitive flexibility the primary areas impacted. Corpus callosum area and thalamic volume were found to be strong MRI predictors of cognitive impairment in the cohort **(Figure 7, next page)**.[190] Regression models controlling for disease duration and age indicated that thalamic volume was a significant predictor of global cognition as estimated by full scale IQ, processing speed, and expressive vocabulary, and was the most robust predictor of cognition relative to other MRI metrics studied.[190] It is interesting to note that cognitive measures were more strongly correlated with MRI variables such as thalamic volume than EDSS or psychosocial outcomes such as depression.

A recent study of 41 patients with POMS investigated whether cortical lesions would distinguish cognitively impaired from cognitively preserved patients with POMS, and found that cortical lesion number, cortical lesion volume and grey matter volume did not differ by cognitive status in this patient group.[191]

Figure 7: MRI Metrics and Cognitive Impairment in Pediatric Onset MS[190]



Since research has shown that adults with MS have regional brain abnormalities associated with memory impairment, Fuentes et al evaluated whether medial temporal lobe structures were vulnerable in POMS.[192] These investigators did not find a significant difference in hippocampal volume between MS patients (n = 32) and age-matched controls (n = 26) despite a significant difference in thalamic volume. Memory impairment was only present in 7% of this POMS patient cohort. In contrast, Rocca et al found that global hippocampal volume was reduced in pediatric MS patients (n = 53) compared with healthy controls (n = 18).[193] These investigators reported that the subregions prominently affected included the cornu ammonis and subiculum, however they failed to find a correlation between these regions and measures of visual and verbal memory.[193]

The cerebellum functions as an associative center for higher order functions including executive function, visuomotor integration, and gait. MS onset during childhood may impact cerebellar function given that pediatric patients have a high infratentorial lesion burden. Weier et al investigated the relationship between cerebellar pathology and cognitive function in youth with POMS.[194] These investigators did not find a difference between patients and controls in cerebellar volume; however regression analysis, which controlled for the volume of the cerebrum, showed that cerebellar posterior lobe volume and infratentorial lesion volume accounted for extra variance on measures of information processing and vocabulary. Lesions in the infratentorial region and the associated impact on vocabulary are a notable difference between pediatric and adult MS.

Given the important role of white matter development in age-related cognitive gains, DTI has been used to investigate white matter pathology and cognition in POMS.[195] Bethune et al conducted a study to compare white matter integrity in children with MS and healthy controls using DTI and to correlate findings with cognitive processing speed.[196] White matter integrity, as measured by fractional

anisotropy, was significantly lower in MS patients vs. controls, particularly in the genu and splenium regions of the corpus callosum, left and right parietal, temporal and occipital lobes. There was a robust correlation between fractional anisotropy in the corpus callosum and SDMT ($P < 0.005$) and visual matching performance ($P < 0.001$) in patients with POMS.[196]

Todorow conducted a study using a global-local hierarchical letter paradigm and DTI to evaluate whether corpus callosum pathology in pediatric MS contributes to less efficient inter-hemispheric transfer of information.[197] Reaction time and accuracy on selective and divided conditions were similar for the MS and the control group except in the situation with response conflict. In this case, reaction time was significantly longer for the patients with MS compared with controls. DTI showed that reduced white matter integrity in the anterior body of the corpus callosum was significantly associated with more difficulty inhibiting task-irrelevant information.[197]

Researchers have looked at the default mode network in POMS for evidence of neural compensation, as in adults there is evidence that functional connectivity is enhanced early in the disease course in patients who are cognitively preserved.[198,82,87]

Akbar et al evaluated resting state functional connectivity and the relationship to brain volumes in cognitively preserved patients with POMS.[199] The study sample included 16 MS patients (mean age 18.7 years, with disease duration 5.3 years) and 15 matched controls. The groups did not differ on cognitive outcomes or brain volumes; however thalamic volume was significantly lower in the patient group. Resting state functional connectivity was assessed using the precuneus as a seed region since it is a major hub of the default mode network, and showed increased activation in the bilateral anterior cingulate cortex, paracingulate and cerebellum in the MS patients compared with controls. Importantly, when functional connectivity was examined relative to structural and cognitive measures, enhanced functional connectivity was associated with less structural brain insult (as measured by lesion volume or normalized thalamic volume). Similar findings were also reported by Rocca et al showing higher resting state connectivity of the right medial frontal gyrus of the attention network associated with lower lesion volume in patients with pediatric MS.[200]

Cognitive Changes in MS and Everyday Life

Faculty: Frederick W. Foley, PhD

EMPLOYMENT

In the general population, employment status has an impact on overall health and well-being.[201-205] In a study published in 1985, Linn et al reported that within 6 months, healthy men who had been fired or dismissed from their jobs had significantly more physician visits, more sick days in bed, were taking more medications, and had worse self-reported health compared with men who were employed.[204] In addition, there is greater incidence of mental health problems such as depression and anxiety within 6 months to a year following unemployment.[202,204] Individuals who are not working engage in more negative health-related behaviors such as substance use and smoking, and unemployment has been associated with increased mortality and greater suicide rates. Conversely, there are benefits in physical and mental health associated with employment and following reemployment. Engagement in the workforce particularly among women results in increased confidence and self-esteem.

Individuals with MS have indicated that they view their work as important to their identity, self-esteem, and social connections.[206] Forty percent of unemployed individuals with MS report wanting to return to work, stating that it is a way of being part of society.[206] In the MS population, it is estimated that 90-96% of individuals are employed prior to diagnosis; however unemployment rates following diagnosis range from 25-80%, with the rates of unemployment highest within the first 5-10 years of diagnosis.[207] It is interesting to note that rates of depression are highest in patients with MS within the first 10 years following diagnosis, which may be a contributing factor to employment status during this same time frame in the disease course.

A number of factors have been linked to unemployment in patients with MS including demographics, disease symptoms (fatigue, physical impairments, balance or walking difficulties, bladder/bowel incontinence, heat sensitivity), and cognitive variables (information processing speed, learning and memory). [208-210] Fatigue is a significant contributor to leaving the workforce for patients with MS (reported by 70-79%), and cognitive difficulties were identified by ~35% of the patients surveyed in a study by Simmons et al as relating to employment loss.[210]

In a study of 312 individuals with MS, LaRocca et al reported that 77% were unemployed; in this sample those unemployed were found to be more disabled, younger, less educated and female.[208] Strober et al examined the employment status, performance on the MSFC and a neuropsychological test battery in a sample of 77 individuals with MS.[211] The authors reported that 48% of the patient sample was unemployed. There were no differences between employed and unemployed patients on demographic variables, however unemployed individuals had longer disease duration and were more likely to have a progressive course. In addition, on the MSFC, there were greater upper extremity difficulties among the unemployed, but no differences between groups on PASAT scores.[211] The cognitive testing showed that there was more impairment on processing speed, learning and memory, and executive functioning among the unemployed patients. In a subsequent study of 101 individuals with MS who were enrolled in a clinical trial on cognition (47% were unemployed), Strober et al reported that EDSS, SDMT, and persistence were the strongest predictors of employment status.[212] Honan et al have also examined cognitive difficulties and employment in people with MS, using subjective and objective cognitive performance tests.[214] In this study of 111 patients with MS, 44% were unemployed, and those unemployed had more impairment on measures of processing speed,

learning and memory, working memory and executive functioning.[213] Morrow et al conducted a study looking at neuropsychological markers of transition from employment to unemployment over 3 years in patients with MS.[214] This study, which included 97 patients with MS, showed 45% experienced a decline in their employment status and that performance on the SDMT and CVLT2-TL distinguished employment status at follow-up. Review of several of the studies evaluating cognition and neuropsychological testing have shown that performance on the SDMT distinguishes employed and unemployed patient groups, with a difference in mean scores between 8-10 points, and effect sizes ranging from 0.80 to 0.90.[206,211-214]

Collectively these studies have shown that demographic and disease variables account for 12-23% of the variance in predicting employment status among persons with MS. Cognitive functioning accounts for an additional 14-20% of the variance related to employment, primarily domains related to processing speed, learning and memory. Much of the variance between employed and unemployed groups remains unexplained and may be due to a range of other person-specific factors. Vocational rehabilitation efforts are imperative, particularly early in the disease course to support individuals with MS and to help these persons remain in the workforce. Cognitive rehabilitation efforts directed at processing speed, learning and memory are likely to be particularly beneficial for those patients experiencing work difficulties.

ACTIVITIES OF DAILY LIVING

Three areas are typically encompassed in activities of daily living (ADLs) in the context MS. These include personal ADLs (self-care skills), instrumental ADLs (tasks that require both motor and cognitive skills for completion, such as cooking, driving, managing money), and advanced ADLs (that also relate to participation, such as employment, community integration, volunteer work). Limitations in ADLs can be conceptualized as an individual's inability to participate in various activities due to a confluence of medical and psychosocial comorbidities. Some people with MS are minimally affected, while others may progress rapidly to total disability with regard to ADLs. Impairments in ADLs are estimated to occur in two-thirds of people with MS.[215] Motor functioning, sensory processing, cognitive functioning, psychological functioning and social functioning all contribute to the ability to perform ADLs, and limitations in these various domains may be present in persons with MS.

There is a strong correlation between cognitive functioning and performance of ADLs, however consensus is lacking about the best approach to the assessment of ADLs in persons with MS. Studies of everyday life activities have been significantly limited in MS, most notably by a lack of reliable and sensitive measures of everyday life functioning. Self-report questionnaires may introduce bias due to affective symptomatology and perception. Performance-based measures that use a sample of behaviors may not reflect the needs or tasks of everyday life for patients with MS (for example, some people may not normally cook). A study by Goverover et al examined the relationship between subjective and objective measures of ADLs in persons with MS.[216] The Executive Functions Performance Test (EFPT) was used as an objective measure of performance of instrumental ADLs; subtests on the EFPT include simple cooking, using the phone, complex cooking, taking medication, paying bills, and hand washing. These authors found that there was a significant difference between healthy controls and patients with MS on the total EFPT score and taking medication and paying bills subtests.[216] Correlations between performance on the EFPT and cognitive measures were significant for processing speed and new learning on the medication, bill payment and complex cooking tests. Executive control was significantly correlated with all subtests except for hand washing. There was no correlation between the objective and subjective measures of functional performance in this study.[216] A subsequent study evaluated factors that moderate activity limitation and participation for persons with MS.[217] In this

study of 72 participants with MS, individuals were grouped based on whether they cooked or not via self-report. There was a significant difference between cookers and non-cookers on working memory (PASAT), processing speed (SDMT), and verbal memory (SRT), and in regression analysis these variables were significantly correlated with cooking level.

Actual Reality (AR) is an innovative performance-based assessment approach for ADLs that involves utilization of the internet to perform actual everyday life activities.[218] This novel approach incorporates three tasks: 1) booking an airline ticket to Florida (United.com); 2) purchasing cookies (cookiesbydesign.com); and 3) ordering pizza (pizzahut.com). The AR study design involves testing on two separate days separated by 3 weeks in which tasks are alternated and repeated. Scoring encompasses cognitive skills, step errors, the number of errors committed and the time to complete the task. Goverover et al conducted a study in which participants performed AR tasks and also were administered the Minimal Assessment of Cognitive Functioning in MS.[218] The authors demonstrated that performance on AR was significantly correlated with performance on the SDMT. Goverover et al have concluded that processing speed as measured by the SDMT is the most constant and common cognitive capacity related to performance of many ADLs.[215]

CONFOUNDING FACTORS

Total lesion load, grey matter hypointensities, and atrophy are closely associated with cognitive impairment in patients with MS, with grey matter atrophy more closely associated with cognitive dysfunction than white matter anomalies.[219,220] However, these primary influences or structural neuropathological variables account for less than half of the variance in cognitive dysfunction in MS; therefore there is great interest in understanding other influences on cognitive impairment.[220] Secondary influences or confounding factors that may be contributing to cognitive impairment in MS include depression, anxiety, fatigue, visual acuity problems, or motor impairment. Establishing a relationship between such confounding factors and cognitive impairment is important because treatment of these secondary influences may minimize some of the cognitive difficulty experienced by patients with MS, and even if not treatable, awareness of secondary factors can provide a more accurate picture of true cognitive dysfunction.

Approximately 50% of patients with MS will have clinically diagnosed depression at some point in their disease course (this compares with ~8% in the general population).[221] Depression in patients with MS is significantly associated with deficits in speeded attention, working memory and planning.[222-224] Depression and anxiety are highly comorbid conditions, and the lifetime prevalence of anxiety in the MS population is approximately 30-50%.[225,226] While the literature on anxiety and cognitive impairment is limited in the MS population, a few studies have reported an association. In a study of cognition and mood in patients with early MS (mean duration of 2.6 years), Simioni et al reported that patients with cognitive impairment had significantly higher anxiety scores compared with those who were cognitively preserved.[227] Julian et al evaluated the relative contribution of anxiety and depression to cognitive functioning among 77 persons with MS.[228] Regression analyses in this study indicated that both depression and anxiety independently were associated with performance on a measure of executive functioning, and when depression was controlled, anxiety was significantly associated with cognitive functioning in this sample.

Severe fatigue is reported by over 75% of patients with MS.[229] In a sample of 45 individuals with MS and 14 healthy controls, Krupp et al used a 4-hour session of cognitive testing (baseline testing and follow-up) to determine whether cognitive fatigue could be identified in MS.[230] These investigators showed that individuals with MS showed a decline on measures of verbal memory and conceptual planning at the end of the testing period, compared

with the control group who showed improvement (practice effect).[230] Bruce et al explored whether response time variability is associated with cognitive fatigue in MS, as response time variability has been shown to be associated with frontal systems dysfunction, decreased white matter volume, and disruptions of thalamic and inferior parietal circuits.[231-234] These authors conducted a study of 87 patients with MS and 24 controls to examine the association between self-reported cognitive fatigue and a measure of response time variability. There were significant differences between the MS patients and healthy controls on fatigue scores and reaction time scores, and a highly significant correlation with increased response variability associated with higher fatigue scores in the MS patients.[231]

Recently, Pokryszko-Dragan et al conducted a study to evaluate event-related potentials and cognition in patients with MS as they relate to fatigue.[235] Patients were grouped by fatigue levels (low, moderate, and severe) and neuropsychological assessment was conducted with the BRB. Patients in the severe fatigue group scored significantly lower than the low fatigue group on tests of memory, visuomotor abilities and attention.[235]

Motor impairments as confounding factors have been studied less frequently in the MS population. MS patients commonly show dysarthria, and many commonly used neuropsychological tests require a rapid spoken response, which may contribute to significantly to poor performance on such tasks.[236,237] Arnett et al conducted a study to examine the extent to which oral articulation problems contribute to performance and group differences on neuropsychological tests for patients with MS.[236] The study sample of 50 patients with MS and 50 healthy controls underwent neuropsychological testing with the PASAT, COWAT, Animal Naming and SDMT tests. Non-oral motor neuropsychological tests were the CVLT-II and the BVMT-R. The Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRR), a commonly used test for rating dysarthria, was used to measure oral motor speed.[238] There were significant differences between groups on all MRR tasks and neuropsychological tasks, with the MS group performing worse than controls. Regression analysis showed that the amount of variance accounted by the group differences was reduced after controlling for MRR performance: SDMT, 10% to 6%; PASAT, 4% to 2%; COWAT, 5% to 2%; and Animal Naming, 11% to 7%.[236] The group effect of overall MRR was nonsignificant with either depression or fatigue as covariates in the regression model.[236] The authors concluded that depression and fatigue may contribute to slowed speech, which then relates to poor performance on neuropsychological tasks requiring a rapid spoken response. Alternatively, slowed speech may be a marker for the level of neuropathology, and therefore is correlated with cognitive test performance because of this third variable association.

It is not uncommon for MS patients to have visual acuity problems, and even mild visual acuity difficulties could impact performance on neuropsychological tests. Bruce et al conducted a study to examine the extent to which visual acuity impacts performance on visually-based tests of complex attention in patients with MS.[239] In this study of 91 MS patients and 25 controls, the SDMT and visual elevator tasks were completed, and visual acuity was measured with the Snellen Near Vision Chart. The results indicated that better visual acuity was associated with better performance on the SDMT and visual elevator tasks ($P < 0.01$ for both correlations), and these associations remained after controlling for age, symptom duration, and EDSS scores.[239]

In a study of 51 patients and 51 healthy controls, Arnett looked at the effects of secondary factors combined on SDMT performance.[221] In this analysis, age and education were the control variables, and secondary factors included visual acuity, oral motor speed, depression, anxiety and fatigue. This approach showed that age and education accounted for approximately 17% of the variance between MS and controls; adding in all of

the secondary factors accounts for another 16% of the variance between groups, which leaves the group difference at ~4%.[221] The authors conclude that secondary factors significantly mediate differences between healthy controls and patients with MS on the SDMT. Consideration and measurement of secondary factors such as depression, anxiety, fatigue, oral motor speed and visual acuity in cognitive evaluations can help to clarify the nature of cognitive impairment in persons with MS.

SOCIAL COGNITION

Cognitive processes are necessary for interpersonal relationships that rely on the capacity to recognize and interpret interpersonal cues that guide social behavior. Social cognition encompasses theory of mind, emotional processing, social knowledge and perception (awareness of the roles, rules and goals that characterize social situations and guide social interactions). Theory of mind refers to mental state attribution, mentalizing or mind reading and can be divided into cognitive and affective theory of mind. Cognitive theory of mind refers to the ability to make inferences about mental states, such as the intentions, dispositions, and beliefs of other people; whereas affective theory of mind is the ability to make affective inferences about what another person is thinking or feeling.[240] Emotional processing includes identifying, understanding and managing emotions, such as facial emotion recognition, affective prosody recognition, emotional awareness, and alexithymia. Dulau et al conducted a study to evaluate the relationship between several dimensions of social cognition and neurocognitive impairment in patients with MS, including RRMS, PPMS, and SPMS.[240] The study sample included 30 patients with RRMS, 15 patients with PPMS, and 15 patients with SPMS. Cognitive impairment in the overall patient sample was noted on information processing speed (75%), episodic memory (55%), working memory (52%), executive functioning (60%), and attention (15%). Overall, combining all MS phenotypes, 43% of patients were impaired for at least one social cognition test, and 20% were impaired on at least 2 tests.[240] Theory of mind was the most frequent social cognition domain involved. Multivariate analyses between theory of mind performance and cognitive characteristics showed significant correlations between executive functions, episodic and short-term memory, and working memory, accounting for 56% of variance on theory of mind performance.[240] Other social cognition domains were found to be less dependent on neuropsychological performance.

Progressive MS and Cognition

Faculty: John DeLuca, PhD

THE INTERNATIONAL PROGRESSIVE MS ALLIANCE

It is estimated that close to half of the 2.3 million people living with MS have a progressive form of the disease.[241] The onset of progression is the main determinant of disability for patients with MS. Despite significant developments over the last 25 years in DMTs for RRMS, people with progressive MS lack effective treatment. A recent survey identified 142 ongoing clinical trials in MS, with a targeted total sample size of 55,758 patients, yet the number of progressive MS patients in these trials was less than 10%.[242] The International Progressive MS Alliance (www.progressivemsalliance.org) was established in 2012 with the mission to expedite the development of effective disease modifying and symptom management therapies for progressive forms of MS.[243] This alliance is a global initiative that aligns MS organizations from around the world, connecting resources and experts to find answers and speed up the development of treatments for people with progressive MS. Four scientific priorities have been set forth by the International Progressive MS Alliance **(Table 7)**.

Table 7: The International Progressive MS Alliance Scientific Priorities[243]

1. Better understand progression so that treatments can be identified and tested
2. Design shorter, faster trials that measure patient outcomes
3. Conduct trials to test agents
4. Develop and evaluate new therapies to manage symptoms and advance rehabilitation

Research projects are being funded through the International Progressive MS Alliance, including Challenge Award grants and Collaborative Network Award grants. Challenge Award grants are short-term pilot studies, and the initial 20 first-round projects are focused on six areas, including clinical trials and outcome measures, biomarkers of progression, gene studies, rehabilitation trials, underlying pathology or progression, and developing new disease models.[243] Three projects have currently been selected for multi-year Collaborative Network Awards. These include, "Identifying a biomarker of disability progression for use in clinical trials," PI Douglas Arnold, McGill University; "Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS)," PI Gianvito Martino, San Raffaele Hospital Milan; and "Development of a drug discovery pipeline for progressive MS," PI Francisco Quintana, Brigham and Women's Hospital.[243] The global research landscape is promising, with increasing investment in research initiatives relevant to progressive MS. For example, encouraging results have been reported recently with the fully humanized anti-CD20 monoclonal antibody ocrelizumab in patients with primary progressive MS (ORATORIO).[244] At ECTRIMS in 2015, Montalban et al reported that ocrelizumab treatment was associated with a 24% reduction in clinical disability progression at 12 weeks vs. placebo.[245] Demonstrated benefits in MRI endpoints and whole brain volume loss were also demonstrated for ocrelizumab treatment compared with placebo. Neuroprotective strategies and autologous haemopoietic stem-cell transplantation are among the other therapeutic approaches currently under investigation for patients with progressive MS.[246,247]

COGNITIVE IMPAIRMENT IN PROGRESSIVE MS

A cross-sectional study published in 1999 reported that 29% of a sample of patients with progressive MS (n = 63) were cognitively impaired (scored at least 2 standard deviations below the control mean on 3 or more tests).[248] On specific cognitive tasks, 43% of patients in this study demonstrated impairment on the SDMT, and 32% were impaired according to performance on the PASAT.[248] In a meta-analysis, Zakzanis evaluated 34 studies that included neuropsychological assessments in patients with MS, including 351 patients with progressive MS (PPMS and SPMS), 656 RRMS, and 858 mixed or not specified; 1265 healthy controls were also included.[249] This analysis showed that the effect sizes for impairment in information processing speed and frontal-executive impairment were greater for patients with progressive MS than RRMS.[249] Several individual studies have reported more cognitive impairment in patients with progressive forms of MS in comparison with RRMS.[250-253] Huijbregts et al investigated cognitive performance in patients with different MS phenotypes and healthy controls.[253] This study showed that patients with PPMS and SPMS performed worse than healthy controls on all cognitive tasks assessed. After controlling for age and gender, patients with PPMS were more impaired than RRMS on tests of information processing speed; however patients with PPMS were less impaired on tests of verbal fluency compared with patients with RRMS.[253] Ruet et al conducted a study to characterize the cognitive abilities of patients with PPMS and RRMS relative to healthy controls matched for age, sex, and education level.[254] In this cross sectional study of 41 patients with PPMS and 60 patients with RRMS, patients with PPMS had worse neuropsychological performance scores and were more impaired on specific cognitive domains than patients with RRMS. Cognitive domains with the greatest impairment in the PPMS group were information processing speed, executive functions, and verbal episodic memory.[254] Differences between the PPMS and RRMS groups remained unchanged after controlling for EDSS score. Further, the authors reported that there was more diffuse cognitive impairment in the PPMS than in the RRMS group, with a greater percentage of patients with PPMS having ≥ 2 cognitive domains impaired (relative to their matched controls) than the RRMS group (47.4% vs. 20.3%, respectively, $P < 0.01$).[254] Ruet et al have also reported mild to moderate correlations between information processing speed and episodic verbal memory and visuoconstruction tests in patients with PPMS.[255]

A longitudinal study of cognition in patients with PPMS was reported by Camp et al.[256] These investigators followed 99 patients with PPMS for 2 years, and showed that while there were no significant differences on mean cognitive scores at baseline and year 2, one third of patients demonstrated decline on individual test scores. Baseline cognitive status was shown to be a good predictor of cognitive performance at 2 years in this patient cohort.[256] Huijbregts et al reported performance on the SDMT at baseline and at 2-year follow-up for patients with PPMS, SPMS and healthy controls.[257] At 2 years, the healthy control group showed improvement on the SDMT, whereas performance by the RRMS group was unchanged, and PPMS group had a small decline in this timeframe.[257]

Several studies have investigated the underlying pathology in patients with progressive MS. Camp et al reported mild-to-moderate correlations between cognitive impairment and T1 or T2 lesion load in 63 patients with PPMS and SPMS, suggesting that cognitive dysfunction in these patients is not fully explained by these pathological changes on conventional MRI.[248] Using DTI, Preziosa et al demonstrated that patients with PPMS showed increases in mean diffusivity, axial diffusivity, radial diffusivity, and decreased fractional anisotropy versus healthy controls.[258] Diffuse injury of the NAWM and cortical demyelination were characteristic findings in patients with primary and secondary progressive MS, as reported by Kutzelnigg et al.[259] Choi et al conducted a comprehensive immunohistochemical analysis on post-mortem brain tissue from 26 cases of PPMS to better understand the extent of perivascular and meningeal inflammation and association with cortical pathology in this progressive form of MS.[260] This study

suggested that generalized diffuse meningeal inflammation and associated inflammation in the subarachnoid compartment has a role in the pathogenesis of cortical lesions and accelerated clinical progression in PPMS.[260] Tur et al have shown strong associations between grey matter magnetic transfer imaging, NAWM volume and T2 lesion load and specific cognitive impairment in patients with PPMS.[261] These authors reported that grey matter magnetic transfer imaging was the main correlate of overall cognitive dysfunction in patients with PPMS. Riccitelli et al described different patterns of grey matter damage and T2 lesions associated with cognitive impairment in patients with different MS phenotypes.[262] Regional grey matter loss correlated with cognitive impairment in each of the MS phenotypes. Unlike patients with RRMS and SPMS, these investigators reported no correspondence between the presence of T2 lesions and grey matter atrophy in patients with PPMS.[262] Functional imaging studies have shown increased activation in the frontal lobes of cognitively preserved patients with PPMS compared with healthy controls, and activation in the parietal and cerebellar regions in cognitively impaired patients with PPMS.[263] Additional studies by Rocca et al suggest that dysfunction of the anterior components of the default mode network may contribute to the cognitive impairment in patients with progressive MS.[264]

COGNITIVE REHABILITATION IN PROGRESSIVE MS

Over the last 25 years, there has been increasing investigation of cognitive rehabilitation in patients with MS, with the vast majority of this work published in the last 5-6 years.[265] However, the percent of patients with progressive MS in these studies is quite low; in fact the number of cognitive rehabilitation studies looking exclusively at persons with progressive MS is zero. Prior to discussing a pilot study of memory training in patients with progressive MS, we will briefly provide a theoretical framework for cognitive rehabilitation in this group of patients with MS. The hippocampus is a key brain structure associated with learning and memory. Sicotte et al demonstrated hippocampal atrophy in patients with MS, with more hippocampal atrophy (including subcomponents of the hippocampus) in patients with SPMS compared with RRMS and healthy controls.[63] These investigators demonstrated a significant relationship between verbal memory and left hippocampal atrophy, including MS patients with lower hippocampal volumes required more learning trials to learn new information.[63] A fMRI study was conducted in patients with MS including an episodic memory task specifically designed to activate the hippocampus. Thirty-two percent of the MS patients were cognitively impaired, with more SPMS cognitively impaired than preserved. Relative to healthy controls, patients with MS who were cognitively preserved showed increased hippocampal network activation during a memory task, in contrast to decreased hippocampal activation in those patients who were cognitively impaired. The authors suggest that the increased hippocampal activation in cognitively preserved patients with MS reflects an adaptive process to prevent cognitive decline, and the functionality of the hippocampal system may deteriorate when this adaptive mechanism becomes exhausted. Such deterioration may be accompanied by decreased brain activation and cognitive deficits. It is within this type of framework that cognitive rehabilitation may have the potential to increase activation of critical networks and offset cognitive decline. Chiaravalloti et al have conducted a pilot study of memory retraining in 21 individuals with progressive MS (17 with SPMS) and objective impairment in new learning.[265] Patients were randomly assigned to either memory retraining or placebo control groups, and the study was conducted in double-blinded conditions. Memory training was associated with approximately 20% improvement on the CVLT relative to baseline, while performance on the CVLT declined in the control group at follow-up relative to baseline. These cognitive rehabilitation results are promising for patients with progressive MS, and previous work by Chiaravalloti et al has indicated that the story memory technique is especially helpful in patients with hippocampal-mediated declarative memory impairment. There is a clear need for more research devoted to cognitive rehabilitation for patients with progressive forms of MS, including Class I studies with larger sample sizes and active control groups.

Conclusion

Cognitive changes in individuals with MS can profoundly impact activities of daily living, vocational and academic pursuits, social functioning, disease management, and overall quality of life. Advances in cognitive assessment, structural and functional imaging, and interventions for cognition, including rehabilitation strategies and exercise hold promise for persons with MS. Patients with MS have individual and wide-ranging needs that are best provided by a multidisciplinary team. Through effective communication and coordination, all members of the MS care team are well positioned to support and improve the quality of care for patients with cognitive issues over the disease course.

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