Cognitive dysfunction in MS: New insights and clinical management
18-19 October 2013 - Taormina, Italy
General information

Venue
This live educational conference takes place at the:

Atahotel Capotaormina
Via Nazionale, 105
98039 Taormina (ME), Italy
Tel. +39 0942 572111
http://www.atahotels.it

Language
The official language of this live educational conference is English.

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Cognitive dysfunction in MS: New insights and clinical management

Serono Symposia International Foundation live educational conference on:

Cognitive dysfunction in MS: New insights and clinical management
18-19 October 2013 - Taormina, Italy

Aim
Cognitive impairment is a debilitating condition that frequently affects patients with multiple sclerosis (MS) even at the very early stages of the disease with a negative influence on quality of life. Since verbal fluency is almost spared, a prompt detection of cognitive dysfunction is challenging thus leading to a delay in diagnosis and treatment. How to detect and follow up cognitive dysfunction in MS and how to treat cognitive decline are still matter of debate, even though controlled studies indicate immunomodulatory therapies were associated with modest cognitive improvement. The aim of the Serono Symposia International Foundation (SSIF) conference on cognition is to review the state of the art in the field of cognition in MS and to handle issues related to pathophysiology, neuroimaging techniques, diagnosis and treatment in order to provide updated knowledge and recommendations for a good clinical practice.

Learning objectives
By attending this live educational conference, the learners will be able to:

- Review the pathophysiological findings underlying cognitive impairment
- Diagnose cognitive impairment with the appropriate assessment tools
- Identify the clinical meaningfulness of cognitive decline, as related to treatment adherence, work capacity, quality of life, and other relevant factors
- Compare the effects of different therapeutic approaches

Target audience
Neurologists, neuropsychologists, psychiatrists and psychologists involved in MS management.

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The CME conference on: “Cognitive dysfunction in MS: New insights and clinical management” held in Taormina, Italy on 18-19 October 2013, is designated for a maximum of 9 (nine) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.

This live educational conference on “Cognitive dysfunction in MS: New insights and clinical management” held in Taormina, Italy on 18-19 October 2013, has been submitted for CME accreditation from the Italian Ministry of Health.

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We value your opinion!

We are continually trying to develop and improve our educational initiative to provide you with cutting-edge learning activities. During this conference you will be asked to answer a real-time survey and after this educational event you will be receiving an online survey to help us to better tailor our future educational initiatives.

We thank you for participating!

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**Scientific programme**

**18-19 October 2013**

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**Friday, 18 October**

8.30  **Serono Symposia International Foundation (SSIF) opening**  
G. Comi (Italy)

8.45  **Welcome and introduction**  
F. Patti (Italy) - M. Zappia (Italy)

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Declared no potential conflict of interest.

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**Bruno Brochet**
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**Anthony Feinstein**
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Francesco Patti  Declared no potential conflict of interest.

Emilio Portaccio  Declared receipt of grants and contracts from Merck Serono, declared the receipt of honoraria or consultation fees from Biogen Idec and Teva. Declared to be member of a company advisory board, board of directors or other similar group: Biogen Idec, Merck Serono.

Maria Assunta Rocca  Declared receipt of grants and contracts from: Fondazione Italiana Sclerosi Multipla, the Italian Ministry of Health. Receipt of honoraria or consultation fees from: Biogen Idec and Serono Symposia International Foundation.

Alan J. Thompson  Declared receipt of grants and contracts: Eisai-funding for PhDs at Wolfson; MS Society UK Research Grant, the receipt of honoraria or consultation fees: Genzyme [honorarium and support for travel]; Novartis, Remedica, SSIF: Invited Lecturer receiving honoraria and support for travel; NIHR-Senior Investigator-honorarium. He declared to be member of a company advisory board, board of directors or other similar group: Chair- Eisai Advisory Board [Clinical Neuroscience] [honorarium to UCL; member IMANOVA Advisory Board; Chair MSIF International Medical and Scientific Board; Trustee, The Brain Appeal, National Hospital Development Foundation stakeholder in a company (including such things as stock ownership, or options to buy, own, or have applied for patents related to a company’s product, receive royalties for previous activities, employment, consultation services, etc.), participation in a company sponsored speaker’s bureau;otherwise benefit from a relationship with a commercial enterprise: Editor-in-Chief, Multiple Sclerosis Journal [Honorarium from Sage Publications].

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Massimiliano Calabrese
Mario Zappia
Abstracts
Abstract not in hand at the time of printing.
Cognitive dysfunction affects many patients with multiple sclerosis (MS) and has been reported even at disease onset. This significant cognitive involvement in MS requires a comprehensively and accurately performed cognitive assessment. We have shown that computerized cognitive testing has the advantages of increased sensitivity due to precise measurement of response time and frequency of errors, minimal ceiling or floor effects due to adaptive testing designs and no learning effects. In a large cross-sectional study that included 1500 MS patients, cognitive performance was poorer than healthy age-and education-matched population norms. We identified that information processing speed and executive functions were the most frequent abnormalities in the MS population with 33.9% and 30.9% of patients performing below one standard deviation of the average, respectively. MS patients with secondary-progressive disease course performed poorly compared with clinically isolated syndrome, relapsing-remitting and primary progressive MS patients. By the fifth year from onset, 20.9% of patients performed below the 1SD cutoff for impairment, p=0.005, and 6.0% performed below the 2SD cutoff for severe cognitive impairment, p=0.002. By 10 years from onset, 29.3% and 9.0% of patients performed below the 1SD and 2SD cutoffs, respectively, p=0.0001. Regression modeling suggested that cognitive impairment may precede MS onset by 1.2 years. Better understanding the epidemiology of cognitive dysfunction and cognitive resilience in MS may help to identify patients at increased risk and facilitate the identification of possible protective factors associated with better cognitive health. Cognitive impairment differed significantly from expected normal distribution at five years from onset suggesting the existence of a therapeutic window during which patients may benefit from interventions to maintain cognitive health.
Cognitive dysfunction affects 40-70% of MS patients. Evidence suggests that these deficits may increase either in frequency or severity in the presence of clinically significant depression. Pseudobulbar affect (PBA) is present in up to 10% of MS patients. Comparisons between MS patients with and without PBA have shown the former to have significantly more cognitive abnormalities. Euphoria, which has a point prevalence of 9-13% in MS patients is associated with advanced disease, a high EDSS score, greater atrophy and lesion volume on MRI and extensive cognitive problems. MS patients who smoke or ingest cannabis have more cognitive dysfunction than patients who do not use the drug. The significance of all these findings is that cognition is often linked to the behavioral changes described. Given that depression, pseudobulbar affect and substance abuse [cannabis use] are all potentially treatable, the possibility of cognition improving as a result must be considered. However, to date, no study in the MS literature has explored this.
Brain pathology and cognition in multiple sclerosis

Multiple sclerosis (MS) causes widespread cerebral white and grey matter lesions, axonal injury, and prominent brain atrophy. As a result, up to 70% of persons with multiple sclerosis (MS) suffer from cognitive impairment (Chiaravalloti & DeLuca, 2008), with such impairments significantly affecting many aspects of a person’s life (e.g., vocational, familial, social, emotional, cultural). However, it is also well known that not all persons with MS suffer from cognitive impairment, even with significant brain pathology. Clinicopathologic research shows only an incomplete (and relatively weak) relationship between disease-related neuropathology (e.g., white matter lesions, cerebral atrophy) and cognitive status (Benedict et al., 2004, 2006). So why are some MS patients better able to cope with significant disease burden without suffering cognitive decline? One potential answer lies in the concept of cognitive reserve which states that persons with higher lifetime intellectual enrichment (often estimated with educational attainment or vocabulary knowledge) are better able to withstand the deleterious impact of increasing neuropathology on cognitive status. This presentation will present data examining the cognitive reserve hypothesis in persons with MS.

Initial work on cognitive reserve showed that MS patients with higher lifetime enrichment are much less likely to show cognitive impairment than MS patients with lower lifetime enrichment, even with the same degree of brain atrophy (Sumowski et al., 2009, 2010a). Using fMRI, MS patients with higher intellectual enrichment have also been shown to display greater cerebral efficiency using than MS patients with lower enrichment (Sumowski et al., 2010b). Further, a recent study which specifically examined cognitive reserve in secondary progressive (SPMS) patients and showed that protective effect of intellectual enrichment on cognitive decline may be greater in more advanced disease (i.e., SP) than earlier relapsing remitting (RR) patients (Sumowski et al., 2012). Two recent longitudinal studies have reported conflicting results on the influence of cognitive performance on long term cognitive outcome (Benedict et al., 2010, Amato et al., 2013).

Clearly, cognitive reserve moderates the relationship between neuropathology based on brain imaging and cognition in MS. Directions for future research will be discussed.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which leads to focal destruction of myelin, acute axonal damage/loss of axons and reactive astrogliosis. The irreversible axonal loss is thought to be the major correlate of chronic disability in MS. MS has long time been considered a focal white matter disease, however, nowadays it is accepted that MS involves the entire central nervous system (CNS), including the grey matter and the normal-appearing white matter. The exact neuropathological correlates of cognitive dysfunctions in MS patients have not been elucidated. Most likely, neuropathological changes in grey matter lesions and the normal appearing brain tissue contribute to this dysfunction. This may include: loss of neurons, loss of synapses and dendrites leading to reduced connectivity as well a generalized atrophy in white and grey matter independent of lesions. These phenomena are discussed in the presentation.
Abstract not in hand at the time of printing.
Data provided by conventional MRI support the notion that cognitive disturbances need to be considered for a more complete clinical characterisation of patients with MS. However, the overall burden of brain MRI-visible lesions does not fully account for cognitive impairment in MS. Indeed, cognitive impairment seems to increase in parallel with the decrease of brain parenchymal volume rather than with the increase of brain lesion load. Furthermore, several MRI studies have highlighted the importance of brain damage in the normal-appearing brain tissue. Gray matter atrophy seems to be the most related to cognitive deficits in MS patients and this holds true since the earliest disease stages. Grey matter damage may evolve most rapidly and might be, to some extent, independent of white matter changes. Such a model of MS argues strongly for the use of these MR biomarkers for an early and accurate assessment and monitoring of cognition in MS.
Abstract not in hand at the time of printing.
Cognitive impairment affects a large proportion of patients with multiple sclerosis (MS) and has a profound impact on their daily-life activities. Improving the knowledge of the pathophysiology of cognitive impairment in MS and of the mechanisms responsible for its evolution over time might contribute to development of better outcome measures and targets for innovative treatment strategies. Functional magnetic resonance imaging (fMRI) provides information about the plasticity of the human brain and, therefore, has the potential to provide important pieces of information about cortical reorganization following MS-related structural damage, which should improve our understanding of the factors associated to the accumulation of progressive disability in this disease. fMRI changes have been described in virtually all patients with MS and different clinical phenotypes when investigating the visual, cognitive, and motor systems. These functional changes have been related to the extent of brain damage within and outside T2-visible lesions as well as to the involvement of specific central nervous system structures. In addition, it has also been suggested that a maladaptive recruitment of specific brain regions might be associated to the appearance of clinical symptoms in MS, such as fatigue and cognitive impairment. Brain functional changes have been shown to be dynamic over time, not only after an acute relapse, but also in clinically stable patients or after drug administration, thus providing an additional paraclinical tool to monitor treatments. fMRI studies from clinically impaired MS patients may be influenced by different task performance between patients and controls. As a consequence, new strategies have been introduced to assess the role, if any, of brain reorganization in severely impaired patients, including the analysis of resting state networks. The enhancement of any beneficial effects of this cortical adaptive plasticity should be considered as a potential target of therapy for MS.
Cognitive impairment can be detected at all stages of Multiple Sclerosis (MS), from clinically isolated syndromes suggestive of MS to advanced stages of progressive MS and even in radiologically isolated syndromes. The choice of the neuropsychological tests employed is critical for determining cognitive deficit. Several batteries have been proposed to evaluate cognitive impairment in MS, and the best known are the Brief Repeatable Neuropsychological Battery of neuropsychological tests (BRB-N) and the Minimal Assessment of Cognitive Function in MS (MACFIMS). These batteries include tests of information processing speed (IPS), attention and memory which are the most frequently impaired functions. Impairment of executive functions could be also evaluated. However detection of cognitive impairment in MS patients in daily practice is not an easy task because applying these batteries to every patient is rarely feasible. Recently a short battery, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) has been proposed. Self-report questionnaires, like the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), and screening by single tests will be also discussed.
Multiple sclerosis [MS] related cognitive disorder is common, and associated with problems in activities of daily living, such as medication adherence, automobile driving, and management of household tasks. The disease is commonly diagnosed in the prime of career development causing a high rate of unemployment. Work disability in MS is a critical factor in quality of life. We are pursuing research to better understand the relationship between neuropsychological [NP] impairment and work capacity.

We have two general goals, one clinical, one methodological. First, we endeavor to track work-related problems more or less continuously so that transient problems can be identified by clinicians before patients lose work. Second, by monitoring work status with more fine-tuned co-primary outcomes, we hope to correlate negative work events with “clinically meaningful”, increments of change on NP metrics.

Regarding the 1st goal, we have begun implementing brief neurocognitive assessments coupled with a web-based, vocational monitoring system. Every three months, patients go to the website and complete three sections:

A. self-reported NP symptoms,
B. general employment information such as hours worked, job responsibilities, salary, etc,
C. work-related problems/accommodations.

Queries regarding work problems and accommodations emphasize behavioral observations rather than subjective evaluations of deficiency. Participants respond with a mouse-click to report negative work events such as formal verbal reprimand, customer complaint, etc, and the O*NET US Department of Labor accommodations are listed for endorsement. The goal is to measure baseline NP and vocational status, and to repeat the former should changes in work status be reported, thereby protecting patients from unfair treatment by employers.

The 2nd goal stems from a recent Topical Review in the MS Journal, focusing on the validity of NP outcomes in clinical trials. Research on clinically meaningful change on NP tests is sorely needed. The FDA offers such guidance related to patient-reported outcomes [PROs], but NP testing is weakly correlated with cognition PROs. Thus, we are left with the task of correlating increments of change on reliable tests such as the Symbol Digit Modalities Test [SDMT] with “anchors” that do not involve subjective judgment. Our work emphasizes correlations between statistically-relevant change on NP tests with changes in clinically relevant anchors such as Work problems or clinical relapses with cognitive impairment. This presentation will summarize our early successes with this approach, highlighting the aforementioned vocational monitoring programme.
Cognitive deficits have a major negative impact on the quality of life of people with MS, but assessment and management is not routinely available outside of specialist centers. A Brief International Cognitive Assessment for MS (BICAMS) has been recommended which takes only 15 minutes, can be used by health professionals without specialist cognitive training and requires only basic materials. The recommendation was based on expert consensus and ratings on psychometric and pragmatic domains.

The recommended battery is the SDMT, the CVLT-II (five learning trials) and BVMT-R II (three learning trials). Additional supporting validation for these scales has become available since the first position paper. A national validation protocol has been published. Currently 25 countries are involved in national validations at various stages.

BICAMS extends availability of cognitive assessment and management to people with MS outside of specialist centres and affords the opportunity of clinic, national and international databases of cognition in MS. Multinational trials investigating cognition will also benefit, as validated scales of known equivalence to measure cognition in MS in many countries become available.
As a chronic disabling disease occurring in young adults in the most productive period of life, multiple sclerosis (MS) determines multiple challenges for both physical and psychological well-being. MS carries specific stressors, such as unpleasant and unpredictable symptoms and accumulation of fixed disability. Patients with MS also face psychosocial consequences of the disease, including disruptions of life goals, social relationships and family projects. Indeed, psychological difficulties are extremely common in MS compared to both healthy populations and other chronic diseases, including elevated rates of depression and distress, increased anxiety, reduced quality of life. High perceived stress correlates and predicts worse adjustment and is important regardless of disease severity. The ability to manage demands and emotions plays a crucial role for people facing with MS. Coping studies consistently show that certain emotion-focused coping such as avoidance and wishful thinking are related to worse adjustment, whereas other strategies, such as positive reappraisal and seeking social support appear to be related to better adjustment. These findings highlight the importance of a comprehensive assessment of MS patients, including psychological domains, mood and coping strategies, all potentially modifiable factors. Orienting therapeutic interventions to those can improve patients’ adjustment to the disease and overall quality of life.
Pediatric onset multiple sclerosis (POMS) is said to comprise approximately 3% to 5% of MS. In the past decade increasing information has become available regarding this condition and therapeutic options for children with MS.

The onset of MS in childhood and adolescence is characterized by a relapsing–remitting disease course, often with high relapse frequency, and with rapid accrual of inflammatory brain lesions in the first few years following the incident attack. Compared to adult onset MS patients, those with pediatric onset disease take nearly 10 years longer to progress to secondary progressive disease and irreversible disability, but they are nearly 10 years younger when they reach disability milestones. Moreover, nearly 30% of patients with POMS will be diagnosed with cognitive impairment within 5 years of MS onset, and emerging data indicate that this impairment is linked not only to a failure of age-expected brain growth but also to a loss of brain volume. These findings illustrate the deleterious effects of MS on the developing CNS, and implicate onset of neurodegeneration even in the youngest patients. The neuropsychological profile of deficits includes impairments of information processing speed, memory, visual-spatial abilities and executive functions as in adults, but also decreased Intelligence Quotient (IQ) and language problems, particularly in subjects who are younger at disease onset. Cross-sectional and longitudinal studies consistently highlight the negative functional impact of these cognitive problems on everyday functioning and academic achievements, also independently of physical disability and clinical relapses. Clinicians should be particularly sensitive to cognitive issues in this population, in order to provide prompt counselling and management strategies.
Identifying and treating cognitive impairment in patients with multiple sclerosis is increasingly recognized as a crucial step in selecting the most appropriate treatment for the individual.

The disease modifying drugs that are licensed for the cure of MS are interferons, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, and more recently teriflimomide, dimethylfumarate and alemtuzumab. All of these drugs have been shown to improve clinical outcomes (relapses and MRI activity) and disability progression.

Many of the pivotal trials did not include cognitive endpoints; then the effects of these drugs on cognition are less clear. In some cases, longitudinal observational studies have been conducted.

It was hypothesized that disease modifying drugs could be effective beyond clinical outcomes, and improve cognitive functions of people with MS. The available studies (very few randomized) and several others, observational and longitudinal seem to demonstrate that immunomodulatory therapies are active in protecting patients with MS to develop cognitive impairment with time. These effects seem to be more prominent when specific treatment starts earlier and with the use of interferon higher dose.
L16. New DMDs and cognition

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Abstract not in hand at the time of printing.
Multiple sclerosis (MS) related cognitive disorder is a common problem and as such there is a great demand for symptomatic treatments. Typically, not all domains of cognitive functioning are impaired in MS. In general, the domains of episodic memory and the speed of information processing, are most often involved. Medical therapies that may improve these deficits have been developed for other clinical populations, and it makes some sense that they may ‘enhance’ abilities in MS patient. This paper addresses the efficacy of these so-called “cognitive enhancers” in MS patients.

One group of studies has employed stimulants to improve processing speed and attention in MS. Negative results were reported for amantadine although trends were noted on sensitive outcome measures. Two studies reported positive effects following single-doses of methylphenidate L-amphetamine, but there is no evidence of a continuous dosing benefit. Evidence for a positive benefit from modafinil is equivocal. A recent double-blind, placebo-controlled study with 121 patients found that modafinil had no convincing effects on fatigue or cognitive dysfunction. In another study modafinil-treated patients showed improvement on an attention test but these results were not replicated.

Krupp and colleagues reported that donepezil improves memory performance and subjective ratings of everyday behaviors over 24 weeks. However, the sample was small and there were a few noteworthy methodological shortcomings in the study. When the design was improved the positive donepezil findings were not replicated. More work is being done to determine if patients with severe memory problems responded better than the mildly affected patients in the study.

Altogether, research in this area suggests only possible benefits of symptomatic drug treatments for cognitive impairment in MS. There are as yet no indicated therapies. Some positive results have been reported, but most often followed by a failure to replicate. The many challenges in this area of the literature will be discussed.
Cognitive impairment is a major and significant problem in patients with multiple sclerosis (MS). MS patients frequently demonstrate various degrees of cognitive impairment mainly involving executive functions and information processing speed even early in the disease course. These difficulties progress over time and can inversely affect patients’ daily activities and quality of life. e-Cognitive remediation is a non-biological treatment that aims to improve cognitive skills through brain training by repeated exercises through engagement in a particular cognitive exercise. The scientific support for beneficial outcome of brain training thrives on the expected effects of neuro-plasticity, a change in neural structure and function in response to experience or environmental stimulation. To better understand the scientific evidence of brain-training through e-Cognitive remediation we evaluated the correlations between various cognitive tests and cognitive remediation tasks in relation to brain magnetic resonance imaging (MRI, high-resolution 3.0 Tesla system, GE scanner, HDX) in 133 MS patients (97 females, mean±SE age 39.2±1.02 years, disease duration 9.5±0.66 years). We demonstrated that both the accuracy and time of specific cognitive remediation tasks correlated with disease duration and neurological disability. Better cognitive performance was associated with higher accuracy and shorter time required for the cognitive remediation tasks. Image analysis disclosed that T1 lesion load that signifies chronic damage correlated with both the accuracy and time of specific cognitive remediation tasks. These data could lead to further research to evaluate e-Cognitive remediation using targeted training programs to improve patients’ cognitive performance, daily activities and quality of life.
It is now well established that up to 70% of persons with multiple sclerosis (MS) suffer from cognitive impairment (Chiaravalloti & DeLuca, 2008). Such impairments can have a significant impact on everyday functional activity in persons with MS. It is generally accepted, although not absolute, that cognitive impairment is more severe and encompasses a greater range of cognitive involvement in progressive MS (especially secondary progressive SPMS) than relapsing-remitting MS (RRMS). Nonetheless, most research on cognitive rehabilitation has been conducted in RRMS. Given the frequency and degree of cognitive involvement in persons with MS, and it affects so many aspects of a person’s life [e.g., vocational, familial, social, emotional, cultural] the need for cognitive rehabilitation therapies and programs is clear. This presentation will present the research data on the effectiveness of cognitive rehabilitation in persons with MS.

Compared to studies in stroke and traumatic brain injury, relatively few studies of cognitive rehabilitation exist in persons with MS (O’Brien, 2008). Two recent Cochrane reviews on cognitive rehabilitation (Rosti-Otajavi & Hamalainen, 2011; das Nair et al., 2012), yielded mixed conclusions. Rosti-Otajavi & Hamalainen concluded that “12 of 14 studies showed some evidence of positive effects of neuropsychological rehabilitation”. However, das Nair (2012), which only included RCT’s limited to memory rehabilitation, found only 4 studies and concluded that there was no support memory rehabilitation. Such reviews of cognitive rehabilitation research have concluded that there is a low level of evidence to support such rehabilitation at this time in persons with MS, primarily because of the low number of studies and several methodological problems in design. However, beyond the Cochrane approach, there is modest support that behavioral interventions can significantly improve targeted cognitive processes. This is especially true in the area of learning and memory where targeted interventions designed to improve the strength of the acquisition of information can significantly improve performance (DeLuca & Chiaravalloti, 2011). Recent studies have also shown that cognitive rehabilitation for impaired learning and memory not only improves neuropsychological functioning, but also results in increased functional brain activity on fMRI and functional connectivity in the brain, as well as improved everyday life activity and quality of life. There is also emerging support for behavioral interventions to improve attention and executive functioning in persons with MS (Sumowski et al., 2010, Goverover et al., 2011, Leavitt et al., 2012). Unfortunately, there are no studies on the rehabilitation of impaired processing speed.

There is also preliminary evidence that physical activity (e.g., aerobic fitness, exercise training) may be associated with improved cognition in MS. One small study found that cardiovascular fitness was associated with improved processing speed, sustained attention and working memory (Prakash et al., 2007) while another showed that such fitness resulted in greater white and grey matter integrity and processing speed (Prakash et al., 2010). However, yet another RCT showed no effect (Oken et al., 2004). Nonetheless, the notion that physical activity may improve cognition in MS deserves further research.
L20. The role of MRI in assessing cognitive rehabilitation

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MS-related cognitive dysfunction is heterogeneous among patients with a variable evolution from one patient to another. Memory and learning dysfunctions as well as slowed information processing speed are among the most common cognitive deficits in patients with MS. However, deficits of complex attention and executive functions are also frequently described. The functional consequences of MS-related cognitive impairment have a multidimensional impact on patients’ activities of daily life (physical independence, employment, social and recreational activities, driving skills and physical rehabilitation outcome). Alleviation of the harmful effects caused by these deficits should be a major goal of MS research and practice. Cognitive rehabilitation is one of the possible treatment strategies, but the real efficacy of such an approach is still debated. This is mainly due to the heterogeneity of the available studies in terms of patients’ inclusion/exclusion criteria, cognitive profiles and outcome measures chosen, as well as study design and follow up duration. MRI has the potential to provide useful metrics to predict patients’ outcome following cognitive rehabilitation, monitor patients’ response and improve the understanding of the mechanisms associated to positive or negative effects of specific programmes.

fMRI studies have shown that cognitive rehabilitation enhances plasticity processes in the brain, thus contributing to reduce the clinical expression of cognitive symptoms. Rehabilitation of memory and executive deficits has been demonstrated to have positive effects on cognitive outcomes with a significant association between cognitive improvement and resting state functional connectivity modifications of cognitive-related brain regions. Enhanced neuroplasticity has been also detected during active cognitive tasks.

Modifications of brain structure following cognitive rehabilitation have been marginally addressed. A cognitive rehabilitation program of attentive and executive functions showed no structural changes in the grey matter and normal-appearing white matter of treated patients over a three months period, suggesting that their structural plasticity might be impaired. Another study demonstrated that the degree of brain atrophy is an important predictor of the effectiveness of a cognitive intervention programme.
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