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FUNCTIONAL AND MORPHOLOGICAL CORRELATES OF COGNITIVE AND SOCIAL COGNITION IMPAIRMENT IN MULTIPLE SCLEROSIS A LONGITUDINAL STUDY

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ABSTRACT

Multiple sclerosis (MS) is the prototype of demyelinating diseases, in which both gray and white matter (GM/WM) pathology contribute to impairment of several cognitive domains including attention, mental processing speed, memory, executive and visuospatial functions, as well as many aspects of social cognition. Such deficits have been reported in all stages and subtypes of the disease, and result in significant, negative consequences for mood and quality of life of people with MS.

The main goal of the current magnetic resonance imaging (MRI) study was to investigate the effects of MS on cognition and brain structure, by combining neuropsychological and morphological investigations. More precisely, we aimed to analyze changes of main cognitive functions over time in mild and early relapsing-remitting MS (RRMS) outpatients compared to healthy subjects, and correlated these findings to GM regional volume changes. We were also interested to explore the impact of MS on many aspects of social cognition, mood, fatigue, psychological well-being, and quality of life of these patients between the beginning and the end of the study.

The first important MRI result was the identification of a right temporal atrophy pattern (inferior temporal gyrus and middle temporal gyrus) in the RRMS group compared to normal controls, which was unchanged between the baseline and follow-up. After one year, a considerable atrophy in deep GM of right hemisphere (amygdala, globus pallidus and putamen) and cerebellum (14.2%) emerged, while disappeared in the left putamen and insula. In addition, the GM volume of the patients at one year was predicted by sex, age, and processing speed (i.e., Symbol Digit Modalities Test).

As for the cognitive evaluation, primary results highlighted that a large proportion (about 50%) of the RRMS group was significantly impaired compared with controls on short- and long-term memory, processing speed, visuospatial and executive functions, and negative emotions (sadness and anger). Patients also showed symptoms of psychological distress (somatization, obsessive-compulsiveness, hostility, and interpersonal problems). These impairments in the RRMS group tended to flatten over time. While long-term memory, perceptual and spatial visual skills, and the anger attribution seemed to improve; deficits in working memory, processing speed and interference inhibition, and the

recognition of sadness remained stable after one year. At the follow-up, characteristics of psychological distress were also reduced, but new depressive symptoms emerged.

Correlational analysis showed a significant relationship between cognitive measures and different cortical and deep structures of GM/WM volumes. Poor memory performance was related to GM reduction in fronto-temporal areas and cerebellum. Executive and speed-based tasks were associated with fronto-temporo-parietal regions in GM. Processing speed measures were also related to posterior parietal-occipital and cerebellar areas of both GM/WM. Finally, some tasks of theory of mind showed a significant association with GM volume of fronto-temporal regions.

Our results highlighted that there was a minimal but significant cognitive impairment in the RRMS group. The pattern of temporal atrophy found in patients compared to controls could account for their initial deficits. MRI findings also showed that volume changes of the cerebellum may play a key role in MS pathology. After one year, a significant reduction in the cerebellar and deep GM structure volumes could also explain why primary deficits in memory and recognition of sadness remained stable, while the others decreased. All these impairments were not significantly related to other factors, such as mood, fatigue and clinical features of the disease. Although performance in some executive measures probably improved due to 'practice effect', working memory and processing speed were still impaired at one-year follow-up, proving that the short-term progression of the disease has a clinically meaningful impact on these abilities. Even emotional-behavioral aspects had improved over time, leading to a better adaptation to the disease by patients.

In conclusion, MS-related pathology has important effects on many aspects of cognition, emotions and behaviors of patients suffering from this condition. Nevertheless, a mild and early RRMS still has a large room for improvement in which multiple compensation mechanisms can be implemented by patients to cope with the consequences of the disease. Early management of healthcare and pharmacological treatment, which occurs at the initial stage of the disease, may also contribute to the well-being and quality of life of people with MS.

CHAPTER I
Multiple Sclerosis

1.1 Description and clinical features

Multiple Sclerosis (MS) is an immune-mediated inflammatory disease affecting central nervous system (CNS) and spinal cord, characterized by the presence of widespread plaques of demyelination, immune cell infiltration and axonal degeneration (Noseworthy et al., 2000). By definition, the term 'sclerosis' refers to scars (or *sclerae*), better known as lesions or plaques, which are mainly formed in white matter (WM), causing inflammation and inhibition of axonal transmission. A hallmark of typical CNS lesions is the dissemination in both space and time, hence the term 'multiple'. Due to multifocal damage, MS results in a wide spectrum of clinical manifestations ranging from motor symptoms to cognitive and neuropsychiatric deficits, to the point that there are no two individuals with the same symptomatic profile or overlapping disease course (Chiaravalloti & DeLuca, 2008).

The first complete description of MS as *sclérose en plaques* was provided by Jean-Martin Charcot (1868), who identified brain lesions characterized by the presence of phagocytes, reactive gliosis and myelin loss. Charcot recognized this disease as a distinct entity – the three signs of MS now known as Charcot's triad are nystagmus, intention tremor, and scanning speech; he gave it a nosological status, made accurate clinical-pathological correlations, emphasized its frequency, speculated on the pathophysiology, and sought effective treatment. The process of renaming the disease was consolidated with publication of the monograph written by Douglas McAlpine, Nigel Compston and Charles Lumsden (1955), since when the condition has universally been known as

multiple sclerosis. The World Health Organization (WHO, 2008) estimates that MS is one of the world's most common neurological disorders and causes of disability in young adults, with major implications for their quality of life and the financial cost to society.

Most people with MS have a normal or near-normal life expectancy, experiencing little disability during their lifetime. Of these, up to 60% are no longer fully outpatient 20 years after onset and, in rare cases, MS is so evilly progressive that is terminal (WHO, 2008). Typically, MS occurs when individuals are more active and productive in many aspects of their life, forging their career, finding a long-term partner or having children. MS can therefore impact on the social and economic well-being of individuals as well as on their families and partners. Cognitive dysfunction is closely associated with functional status in MS (Chiaravalloti & DeLuca, 2008). The disease is well-known to have a negative impact on daily activities, often leading to loss of gainful employment for many patients, and with a large contribute of cognitive impairment to this high rate. Rao et al. (1991) report that individuals with MS who are cognitively impaired usually participate in fewer social and vocational activities, have greater difficulty in maintaining employment and in doing routine household tasks, and are more vulnerable to psychiatric illnesses than individuals with a purely physical disability — factors that can all affect the overall quality of life of the patient.

MS is a complex and unpredictable disorder, in which important degenerative phenomena are part of the histo-pathological process. According to current opinion, MS represents an autoimmune disease, requiring genetically susceptible individuals to be exposed to a set of environmental agents, which subsequently trigger an auto-aggressive immune attack on the myelin sheath and other components of CNS (Compston & Coles, 2002). MS results in motor, cognitive, and neuropsychiatric symptoms, all of which can occur independently of one another. Despite our awareness of the considerable impact of MS, there is a serious lack of information about the resources available to address it. The WHO (2008) and the Multiple Sclerosis International Federation (MSIF, 2013) undertook a major collaborative project to determine the global epidemiology of MS and the resources to diagnose, inform, treat, rehabilitate, support and provide services to people suffering from this disease. To meet this need, further efforts must still be made to ensure the physical-functional-social-emotional well-being of all people with MS.

1.2 Epidemiology and etiological agents

Although MS can occur at any age, it is usually diagnosed during early adulthood, between ages 20 and 40 and with a peak onset at about 30 years of age (WHO, 2008). The disease is twice as common among women than men (female/male 2:1 ratio), but this gender difference in MS risk is not fully understood. The Atlas of MS 2013, mapping the disease worldwide, published by the MSIF (2013), revealed that the number of people with MS estimated by WHO (2008) has increased from 2.1 million to 2.3 million. Likewise, the median estimated prevalence has risen from 30 in 2008 to 33 per 100.000 in 2013, but it is unclear whether this increase is due to better diagnosis and reporting, or to other causes (**Figure 1**; MSIF, 2013).

The worldwide incidence and prevalence of MS is highly variable due to the role played by both genetic and environmental factors. The greatest incidence tends to be at the extremes of latitude in the northern and southern hemispheres. The influence of geographic patterns is also confirmed by the higher incidence of MS in high-income countries than in rural areas (MSIF, 2013). It is noteworthy that this heterogeneous pattern may partly depend on the unequal distribution of important diagnostic tools or the less availability and accessibility of care facilities, resulting in under-recording of MS in many low-income countries.

While MS is present in all regions of the world, its prevalence varies greatly, being highest in North America and Europe and lowest in Sub-Saharan Africa and East Asia. This variability partly reflects geographic variations in ethnicity. Indeed, the disease is most common in Caucasian individuals than in other ethnic groups, such as Africans, Native Americans, Mexicans, Chinese, and Filipinos (Ramagopalan et al., 2010). In particular, the Scotland and Outer Hebrides are the regions with the highest recorded prevalence rates up to 300 cases per 100.000 (Kurtzke, 2005). In Sardinia, where the population is genetically homogeneous and stable, repeated surveys have shown increasing incidence of MS. In contrast, there are ethnic groups that seem to be resistant to the disease despite living in areas with a relatively high prevalence rate such as Maoris in New Zealand, the Hutterites and Natives in Western Canada (Rejdak, Jackson & Giovannoni, 2010).

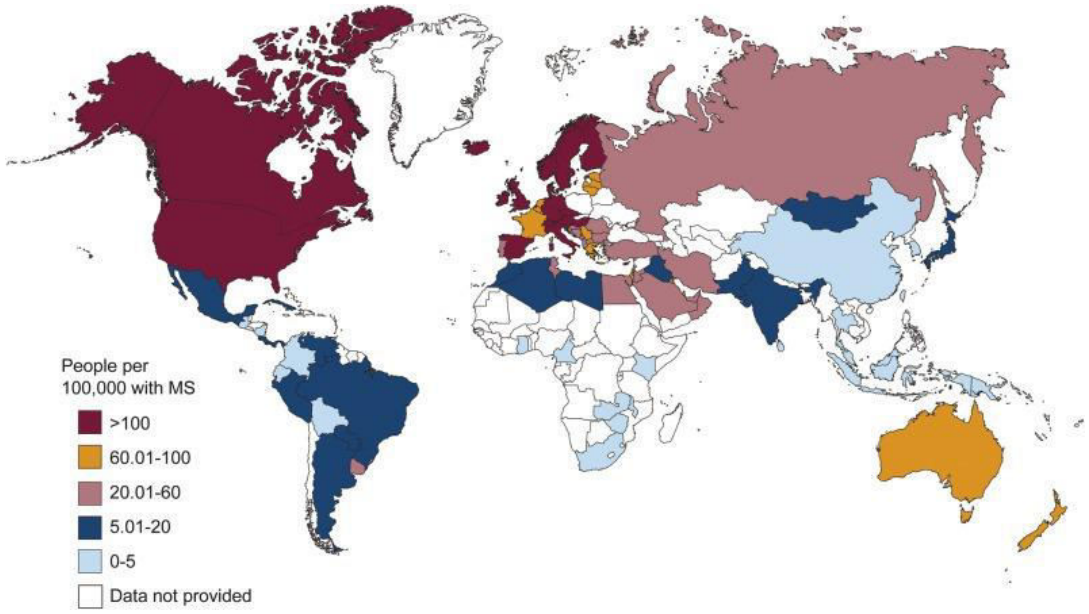

Figure 1. *Worldwide prevalence of multiple sclerosis*. Multiple Sclerosis International Federation, 2013.

Although there is no clear explanation for the differences in the worldwide distribution of MS, these variations appear to be due to the combined role of both genetic and environmental factors. The observation that there are extremely susceptible populations, as well as their exceptions, has immediately drawn the attention on the genetic hypothesis. Studies on family aggregations of MS cases have confirmed that genetic predisposition is not attributable to a single gene, but to a multitude of genes disseminated in different portions of DNA. The incidence of MS in first-degree relatives is twenty times higher than in general population. In monozygotic twins, the concordance rate has been reported to be as high as 30% compared with rates of less than 5% in dizygotic twins, while genetically unrelated family members living in the same environment are of no higher risk than background population (Dyment, Ebers & Sadovnick, 2004).

Extensive genome-wide association studies have identified about thirty loci, related to the modulation of immune mechanisms and responsible for the risk of disease. Among these, the most common alleles associated with MS are human leukocyte antigen

(HLA) haplotype, which encodes for molecules that present antigen to $CD4^+$ T cells (International Multiple Sclerosis Genetics Consortium, 2007). The HLA system on chromosome 6 has been identified as being consistently linked with MS development in Caucasians (Ramagopalan et al., 2010). In Northern Europeans, the presence of HLA DR2 haplotype is strongly associated with MS, while DR3 and DR4 genes are present in some Southern European populations (Dyment, Ebers & Sadovnick, 2004; International Multiple Sclerosis Genetics Consortium, 2007). This locus is believed to account for 10-60% of the genetic risk for MS (Hillert & Olerup, 1993). Nevertheless, the evidence that this gene cannot be identified with MS is provided by the observation that in some hot-spots areas of the disease there are genetically distant populations (e.g., Sardinia), which exhibit other class II HLA alleles associated with increased MS risk (Marrosu et al., 2001).

Another genetic evidence in the pathogenesis of MS is carried by the involvement of polymorphism of two cytokine receptor genes: the interleukin (IL)-2 receptor α (IL2RA) and IL-7 receptor α (IL7RA) genes on chromosome 10p15 and 5p13, respectively (International Multiple Sclerosis Genetics Consortium, 2007). A further aspect concerns the role played by hormones in triggering MS pathology. This hypothesis was supported by two observations. Firstly, the disease incidence is approximately 2-fold higher in women than in men (Ramagopalan et al., 2010). Secondly, the relapse rate is observed to decrease in late pregnancy (Confavreux et al., 1998). Nevertheless, the mechanisms by which hormones may affect MS expression are still being investigated and genetics alone is not sufficient to explain its etiology.

For MS to be triggered, it is necessary for the subject with genetic predisposition to be exposed to an environmental factor acting as a catalyst for the disease. Migration studies provide an opportunity to study the effect of changes in physical, social and cultural environments on disease risk (Marrie, 2004). By assessing the impact of migration from one country to another as well as within a country, these studies have reported that individuals emigrating from low- to high-risk areas retained the low risk of their origin region, while those moving to low-risk areas had an intermediate risk between their origin and destination areas (Kurtzke, 1993). Data on age at migration suggest the risk of disease is established largely in the first two decades of life (around 15 years), although there is no strict cut-off point (Detels et al., 1978; Kurtzke, 1993).

The viral and infective hypotheses, with a period of latency, have also been formulated. Viral infections induce an inflammatory response associated with interferon-gamma (IFN-γ) synthesis, which is a proinflammatory cytokine with antiviral property that can exacerbate MS. For this reason, it is believed that even the most banal and common viral agents may trigger clinical relapses (Ghezzi & Zaffaroni, 2013). A large number of infective agents have been added to the list of proposed etiologies: measles, human herpes virus 6 (HHV-6), human endogenous retroviruses such as human T-cell leukemia virus type 1 (HTLV-1), *Chlamydia pneumoniae* bacterium, Epstein-Barr virus (EBV), and so on (Ramagopalan et al., 2010; Sospedra & Martin, 2005). The most compelling evidence is provided by the association between EBV infection and MS development. This virus leads to a latent lifelong infection of B-cells and serum levels of antibodies that appear to be increased several years before MS onset (Levine et al., 2005). People with symptomatic EBV infection or with higher antibody responses are at greater risk of developing MS (Ascherio & Munger, 2007; Levin, et al., 2005). This observation is not unique to MS and has been noted with other putative autoimmune diseases. Nonetheless, the actual causal or pathogenic role of this viral agent in MS is still debated.

The geographical and temporal variations in the incidence and prevalence of MS suggest the role of latitude as a potential environmental factor. A possible explanation for the association between latitudinal gradient and MS frequency concerns sunlight exposure and vitamin D levels. As a matter of fact, a strong inverse correlation between ultraviolet radiation levels or past sunlight exposure and MS susceptibility has been reported (Marrie, 2004; Ramagopalan et al., 2010). This interesting hypothesis is based on the close relationship between geographical differences in sunlight exposure and the influence of latitude on MS worldwide prevalence. More precisely, these are the direct effects of sunlight exposure on serum vitamin D levels and the immunomodulatory effects of vitamin D on T-cell homeostasis (Correale, Ysrraelit, & Gaitán, 2009). The main source of vitamin D is exposure to sunlight, but any shortage can also be compensated in the diet. In a prospective epidemiological study on the US Army, a significantly reduced MS risk among white individuals by increasing serum 25-hydroxyvitamin D levels has been demonstrated (Munger et al., 2006). Other environmental factors that may play a role in the susceptibility to MS include diet, cigarette smoking, occupational and social status.

1.3 Pathogenesis

MS is the most common inflammatory demyelinating disease of the CNS, triggered by a $CD4^+$ T cell-driven immune response to destroy the myelin sheath recognized as a foreign body. Traditionally, WM was considered the main site of involvement, but lesions in the cortex and the deep structures of gray matter (GM) have also been found. The pathological hallmarks of MS lesions include the breakdown of the blood brain barrier (BBB), multifocal inflammation, demyelination, oligodendrocyte (OGC) loss, gliosis and axon degeneration (Prineas et al., 2001).

Beyond the already mentioned environmental and genetic risk factors, two models of MS pathophysiology have been hypothesized. The unanswered key question is whether the initial triggering process is a primary autoimmune attack (outside-in) or a cytodegeneration (inside-out), meaning if MS begins outside of the CNS (behind the BBB) or inside it (Stys et al., 2012; Trapp & Nave, 2008). In the 'outside-in' model, MS has usually been considered an autoimmune disease in which deregulated auto-reactive T-cells in the periphery cross into the CNS and, together with macrophages and B-cells, proceed to destroy various CNS components (Herz, Zipp & Siffrin, 2010). This approach, based on the overwhelming evidence that the disease has an inflammatory phenotype, rests on the assumption that the pathophysiology begins with a primary immune dysregulation, according to which a systemic abnormality of the immune system targets the CNS. However, such a model is being challenged by a competing viewpoint arguing that MS is a primary neurodegenerative disease in which the initial malfunction occurs within the CNS, similarly to other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. The 'inside-out' model suggests the primary involvement of a specific cellular damage, probably the oligodendrocyte-myelin complex, and by releasing highly antigenic constituents, secondarily promotes an autoimmune and inflammatory response in the predisposed host (Hauser & Oksenberg, 2006; Trapp & Nave, 2008). Whether it is speculation or not remains to be clarified, but MS is undoubtedly a multifactorial pathology whose developmental outset depends on genetic predisposition, environmental factors and infectious agents.

1.3.1 Demyelination

Myelin sheath is a multilamellar insulating membrane that intermittently wraps neuronal axons and it is produced by the OGCs in the CNS and by the Schwann's cells in the peripheral nervous system (PNS) (Simons & Trotter, 2007). The main function of the myelin sheath is to increase the speed at which impulses propagate along the axon fibers, while the non-myelinated breakpoints of the axons are called nodes of Ranvier in which there is a high density of sodium (Na^+) channels generating action potentials. The myelin is therefore able to isolate the axons and cluster the Na^+ channels in correspondence of Ranvier's nodes, allowing the saltatory propagation of action potentials along myelinated axons from one to the next node (Waxman, 2006).

The focal areas of inflammatory demyelination are seen as plaques in the WM, in which the conduction of electrical pulses down the axons is blocked due to the loss of myelin and to the redistribution of the Na^+ channels along the axons (Trapp & Nave, 2008). The myelin damage is mediated by T-cells and the inflammation is mainly composed of activated microglia and blood-derived monocytes (Siffrin et al., 2010). MS affects the CNS globally: inflammation is not limited to demyelinated active plaques in the surrounding WM but also far from the origin site; the infiltrations of T-cells, B-cells and macrophages are also present in inactive plaques (Lassmann, 1999).

Demyelination therefore leads to an increase in the energy demand of nervous conduction and to an ionic imbalance, thus compromising the production of adenosine triphosphate (ATP) and making the axons more vulnerable to inflammation and degeneration. In the early stages of MS, some degree of re-myelination is possible up to disease progression, in which repeated demyelination of previously re-myelinated areas may lead to an exhaustion of progenitor cells pool and persistent demyelinated plaques (Lassmann, 1999).

1.3.2 Immunopathological appearance of demyelinating lesions

Brain lesions, known as plaques, in MS are constantly in the process of formation: some of them may regress during the course of the illness as well as the onset of new lesions in

a long history of disease can be experienced. The pathological hallmark of plaques, which resemble scars, is the presence of perivascular lymphocytes, altered OGCs and astrocyte activation. Macroscopic lesions are most commonly seen in the spinal cord (50%), optic nerves (25%), brainstem/cerebellum (20%) and periventricular WM (Rejdak, Jackson & Giovannoni, 2010). The features of individual lesions vary and depend on the location, age, and presence or absence of regeneration. MS lesions are typically divided into three pathological categories, according to inflammatory activity determined by the density and distribution of macrophages and microglia (Lassmann et al., 1998).

Acute active plaques are characterized by infiltration of myelin-laden macrophages, T-cells, activated microglia associated with a low degree of infiltrating lymphocytes. Recently, active lesions have been further classified into different pathological subtypes based on the type of inflammatory reaction, the involvement of immunoglobulin and complement, the expression of myelin proteins, the morphology of the plaque edge, and the patterns of OGC injury (Lucchinetti et al., 2000). Pattern I shows active demyelination associated with infiltration of T-cells and macrophages, and often re-myelination. Pattern II is similar to pattern I with the additional deposition of immunoglobulin, activated complement and antibodies on degenerated myelin sheaths. Pattern III displays activated microglia, without immunoglobulin deposition and complement activation, OGC apoptosis with preferential loss of myelin-associated glycoprotein (MAG). Pattern IV contains T-lymphocytes, microglia and macrophages, and reveals OGC death. Among them, pattern II is the most frequent (about 58%), followed by pattern III (about 26%), pattern I (about 15%) and pattern IV (about 1%). Whether or not these pathological subtypes represent different stages of the disease or autoimmune or toxic/viral variants is still a speculation.

Chronic active plaques usually display microglia activation, moderate lymphocytic infiltration and immunoreactive macrophages for myelin degradation products, which accumulate along the sharply defined edge of the lesion. Demyelination, hypertrophic astrocytes and some damaged axons are also present.

Chronic inactive plaques are hypocellular scar-like lesions characterized by astroglial scars, no macrophages containing myelin degradation products, reduced number of demyelinated axons, and limited inflammatory infiltrates.

The development of advanced magnetic resonance imaging (MRI) techniques has allowed to identify specific white and gray areas without lesion signs but predisposed to developing them. These areas referred to as normal-appearing (NA) WM and GM show a normal appearance of myelin but also display signs of microglia and astrocyte activation (Kutzelnigg et al., 2005, 2006). The NAWM characteristics are not well-defined yet, although there is great consensus about the hypothesis that these areas are preferentially exposed to lesion development (Allen et al., 2001; Kutzelnigg et al., 2005, 2006). Recently, particular interest has focused on the demyelination of the cerebral cortex, which associated with cortical atrophy, has been recognized as an important component of MS pathology. Post-mortem studies have revealed that extensive cortical demyelination is typically present in patients with progressive disease (Lassmann, 2012). Both cortical and NAWM pathology, reflected by widespread axonal injury with profound microglia activation, occur on the background of a global inflammatory response in the whole brain and meninges (Kutzelnigg & Lassamann, 2006). Three main types of cortical lesions have been described: cortico-subcortical (leukocortical) lesions, affecting the cortex and adjacent WM, small and purely intracortical lesions and band-like subpial lesions directly abutting on the subarachnoid space (Bø et al., 2003). It was initially believed that cortical lesions differed from WM lesions – for the absence of perivascular and parenchymal T- and B-lymphocytes as well as vascular inflammation and BBB disorder – and were only developed in the progressive stage of the disease. Lucchinetti and coworkers (2011) have shown that GM lesions also appear since the initial stage of the illness and are characterized by lymphocytic infiltrations, as in WM lesions. Inflammatory cells are also found in the meninges, which is compatible with the appearance of active cortical plaques observed in primary and secondary progressive MS (Choi et al., 2012). These findings support the hypothesis that meningeal inflammation causes tissue damage to the cortex by two different mechanisms. On one side, activated T- and B-lymphocytes may directly affect the cells within the infiltrated area; on the other, the cytokines and chemokines released by lymphocytes, macrophages and microglia may spread more deeply into the tissue, destroy cell homeostasis, and induce neurodegeneration and demyelination even away from the infiltration area.

Demyelination could be overcome by endogenous mechanisms fostering the generation of new myelin and promoting the formation of so-called ‘shadow plaques’.

These areas appear to be distributed as typical lesions of MS, but are characterized by subtle myelin sheaths with enlarged internodes. The re-myelination process depends on the stage of the disease and on the position of the lesion. It is a known fact that lesions in the subcortical WM or in the cortex are generally more prone to re-myelination, when compared to periventricular lesions (Albert et al., 2007; Patrikios et al., 2006).

1.3.3 CNS autoimmune response

Genetic susceptibility and exposure to an environmental agent in childhood induce auto-reactive T-cells. After a latent period, a systemic trigger activates these auto-reactive T-cells, which cross the BBB selectively and on re-exposure to their auto-antigen initiate a cell-mediated inflammatory reaction (**Figure 2**; Rejdak, Jackson & Giovannoni, 2010).

Once activated by antigen-presenting cells, T-cells proliferate and produce a range of pro-inflammatory cytokines. These cytokines activate local microglia, astrocytes and endothelial cells, which in turn produce other cytokines, such as IL-1 and tumor necrosis factor-α (TNF-α), involved in systemic inflammation stimulating the acute phase reaction. Sequestered CNS antigens, which are released as a result of tissue damage, initiate further episodes of autoimmune-induced inflammation, recruiting other inflammatory cells into the lesion. Cytotoxic mediators in combination with auto-antibodies, complement activation and the effects of pro-inflammatory cytokines cause OGC death, axonal toxicity, demyelination, and conduction block. Whether (or not) a lesion results in clinical symptoms and/or signs depends on the anatomical site and lesion size as well as on the integrity of the neuronal pathway involved. Immunomodulatory cytokines, e.g. IL-4 and IL-10, and growth or trophic factors, e.g. brain-derived neurotrophic factor, produced by T-cells, subsequently downregulate inflammation and promote the proliferation and survival of OGCs. Axonal plasticity, that is the synthesis of Na^+ channels in demyelinated nerve segments or re-myelination in conjunction with GM plasticity, results in functional recovery. Persistent demyelination leads to a gradual loss of axons, resulting in the development of progressive neurological impairment.

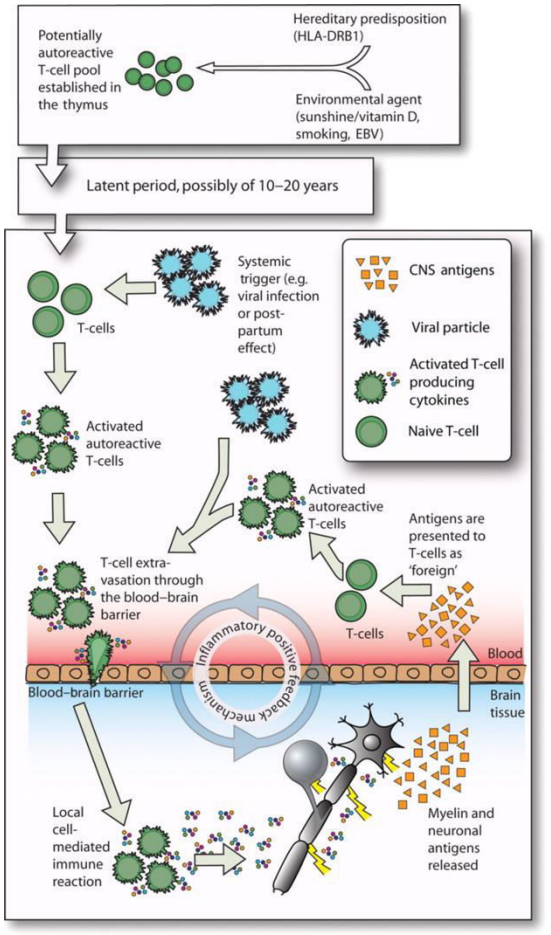

Figure 2. *The proposed pathogenesis and local immune mechanisms in MS*. From Rejdak, Jackson & Giovannoni (2010). *Br Med Bull*, **95**(1):79-104.

$CD4^+$ T cells play a key role in controlling and tuning of both acquired and innate immune responses and, in physiological conditions, these auto-reactive T-cells are monitored by regulatory mechanisms. Under specific conditions, the avidity of auto-reactive T-cells for auto-antigens can be increased, leading to their aberrant pathological activation (Sospedra & Martin, 2005). Various hypotheses have been proposed to explain this mechanism, including microbial infections. Viruses and bacteria have been considered by far as environmental triggers because of their ability to break peripheral tolerance and activate CNS autoimmune responses. However, specific pathogens have not been definitively identified in MS (Ramagopalan et al., 2010).

$CD4^+$ T cells are present in both perivascular spaces and cerebrospinal fluid (CSF) in individuals with MS (Sospedra & Martin, 2005). The detection of antigen-specific

$CD4^+$ T cells has revealed that T-cells responsive to myelin antigens are present at the same frequency in MS and healthy subjects (Pette et al., 1990). It has been proposed that auto-reactive T-cells in healthy individuals may provide important inflammatory signals and neurotrophic factors for post-injury neuroprotection (Moalem et al., 1999) or promote neurogenesis and spatial learning skills in adulthood (Ziv et al., 2006). The most compelling proof that myelin-reactive T-cells can induce inflammatory demyelination is provided by targeting of $CD4^+$ T cells by a direct monoclonal antibody (alemtuzumab, also known as Campath-1H). This results in a deep reduction in disability and inflammatory activity in relapsing-remitting but not secondary-progressive MS (Hauser & Oksenberg, 2006).

The immune-mediate myelin attack has long been considered the major event in MS pathogenesis, assuming that inflammation was the forerunner of the whole course of the disease. Recently, MS has been found to be a much more complex disease than originally assumed, in which the main cause of irreversible neurologic disability is the loss of axons following acute attacks (Dutta & Trapp, 2007). However, the association between inflammation and axonal pathology is still controversial and investigations are currently ongoing.

1.3.4 Axonal degeneration

An important pathological feature in relation to MS is the ongoing axonal loss, which is responsible for the irreversible disability and the progression of the disease. Axonal pathology and transection is demonstrated in both acute and chronic MS lesions (Bjartmar, Wujek & Trapp, 2003). The observation of a significant axonal transection in patients with a short-disease duration, i.e. when inflammatory demyelination is predominant, has shown that axonal loss occurs from the onset of the disease. Axonal loss hence takes place in association with the early inflammation in the disease and continues at different levels of intensity throughout the course of the illness.

Several non-inflammatory and inflammatory mechanisms contribute to the degeneration of axons. As main effector cells of the innate immune response involved in axon damage, activated microglia and peripheral-derived macrophages release toxic

substances, including pro-inflammatory cytokines (TNF-α and IL-1), oxygen radicals and nitric oxide (Ransohoff & Perry, 2009). These substances discharged into CSF and urine play a role in many features of the disease: BBB breakdown, OGC injury, inhibition of mitochondrial respiration affecting energy metabolism and ATP synthesis, changes in Na+ channels distribution causing axonal conduction block, accumulation of intra-axonal calcium and cytoskeleton disruption (Smith & Lassmann, 2002).

Another mechanism that could determine axon damage is the loss of myelin and OGC derived trophic support. Indeed, myelin and OGCs are highly trophic factors and their loss has an impact on axonal function, phenotype and survival (Wilkins & Scolding, 2008). These functional and structural changes may all destabilize and predispose the axon to degeneration. Once the axon loss threshold is reached and the CNS compensatory capacity is exceeded, irreversible neurological disability becomes clinically evident (Dutta & Trapp, 2007).

Initial axonal loss may not have an immediate clinical impact in the early stages of the disease, but accumulation of further lesions over time may lead to irreversible neurological disabilities typical of MS progression. Indeed, conversion from the relapsing-remitting to secondary-progressive form is thought to occur when the brain exhausts its ability to further compensate for axonal loss (Nave & Trapp, 2008). Consequently, the strategies to promote re-myelination and recovery of saltatory conduction are only effective if axons are spared. From this standpoint, understanding the cellular and molecular mechanisms of axonal transection along the progression of the disease is indispensable to pave the way for new neuroprotective therapies (Dutta & Trapp, 2011).

The axonal degeneration may occur independently from the demyelinating plaques. It is still to be determined whether the inflammatory response is a primary event or a secondary reaction to the degeneration of axons (Wilkins & Scolding, 2008). As the disease worsens, the MS brain continuously undergoes atrophy in the absence of inflammation. To determine the cause of permanent neurological disability in MS, the attention of clinicians has been focused on the role of axonal pathology and neurodegeneration. It seems that the two processes, inflammatory and neurodegenerative, may run parallel and may be independent of each other, thus challenging existing concepts and breaking new ground on the causes of the disease (Trapp & Nave, 2008).

1.3.5 Gut microbiota role

In the last 50 years, our lifestyle has led to a lower biodiversity of the microbiota (dysbiosis), i.e. the bacteria residing in the intestine. The gut bacterial flora, besides helping the digestion of food and the absorption of nutrients, is of fundamental importance during the development of the immune system. It can be influenced by many factors such as nutrition, hygiene, smoking, exercise, stress, sun exposure, antibiotic use, and even proximity to pets. In Western countries, improved sanitation has led to an increase in the incidence of autoimmune diseases, which are almost unknown in developing countries, such as Africa. Some microorganisms of the intestinal bacterial flora, present mainly in industrialized countries, irritate the immune system and activate it at the limit of control, thus creating the favorable conditions for the onset of autoimmune diseases such as MS (Battistini & Borsellino, 2017). In the last few years, data on the effects of the gut microbiota composition on many diseases have increased, and this has become one of the 'hottest' topics for scientific research. There is growing evidence of population differences in the intestinal microbiota, consistent with modest dysbiosis, in multiple human autoimmune diseases (Gevers et al., 2014; Scher et al., 2013), including MS (Cantarel et al., 2015; Jangi et al., 2016; Miyake et al., 2015). Furthermore, microbiota have been shown to mediate the regulation of immune responses in experimental autoimmune encephalomyelitis (EAE), the pre-clinic mouse model of MS (Berer et al., 2011; Lee et al., 2011).

Two recent papers, published by a research group at the University of California (Department of Neurology, San Francisco) and Germany (Max Planck Institute of Neurobiology, Martinsried), have shown for the first time that intestinal flora from patients with MS can trigger an MS-like illness in an animal model (Berer et al., 2017; Cekanaviciute et al., 2017). Researchers have found that gut microorganisms were able to activate T-cells in genetically modified autoimmune mice, causing the development of brain lesions similar to those found in MS. The first study examined the gut microbiota from monozygotic twin pairs, in which only one twin had MS. No significant differences were observed between the two siblings but between different families, suggesting that intestinal bacteria are more influenced by the diet and the geographical area of origin. When the researchers transferred the gut microbiota from the twins into transgenic mice

expressing a myelin autoantigen-specific T-cell receptor, they found that MS twin-derived microbiota induced a significantly higher incidence of autoimmunity than the healthy twin-derived microbiota. Gut bacteria from MS patients also seemed to block the production of molecules, like the cytokine IL-10, that reduce inflammation, suggesting that the components of the human microbiota contribute to CNS-specific autoimmunity (Berer et al., 2017). The second study, by Cekanaviciute et al. (2017), analyzed the immunoregulatory effects of human gut microbiota of 71 people with MS and 71 healthy individuals. The authors found that two bacterial groups, Acinetobacter and Akkermansia, were significantly associated with MS, inducing pro-inflammatory responses in patients and in monocolonized mice. Another group, Parabacteroides, which was reduced in MS patients and abundant in healthy individuals, stepped up protective regulatory immune actions in mice. Finally, microbiota transplants from MS patients into germ-free mice resulted in more severe symptoms of EAE and reduced proportions of IL-10+ Tregs compared to 'humanized' mice with healthy control microbiota.

Another intriguing Italian study, using 16S ribosomal RNA sequencing, analyzed the microbiota in the small intestine of 19 relapsing-remitting MS patients and 18 healthy subjects (Cosorich et al., 2017). Disease activity in the relapsing-remitting form is correlated with the periodic activation of myelin-specific T-cells, but the mechanisms that regulate their aggressiveness are still largely unknown. T helper 17 (TH17) cells play an important role in MS pathogenesis, and EAE studies demonstrate that effector TH17 cells triggering brain autoimmunity originate in the intestine. Although several B and T subsets participate in disease pathogenesis, effector TH17 cells represent the first wave of pathogenic T-cells infiltrating the CNS, due to their ability to efficiently breach the BBB, contributing to the damage of the myelin sheath (Kebir et al., 2007; Korn et al., 2007). Cosorich et al. (2017) found that in patients with relapsing-remitting MS, there is a selective expansion of effector TH17 cells in the small intestinal mucosa that is linked with specific microbiota modifications. In particular, MS patients with high disease activity and increased intestinal TH17 cell frequency showed two conspicuous anomalies: a small amount of Prevotella, a bacterium that reduces the differentiation of lymphocytes in TH17 cells as well as an increase of two strains of Streptococcus (S. oralis and S. mitis), which usually reside in the oral cavity and have remarkable inflammatory capacity. The Italian study demonstrates that brain autoimmunity is associated with specific microbiota

modifications and excessive TH17 cell expansion in the human intestine (Cosorich et al., 2017).

It has long been suspected that bacteria in the natural intestinal flora may be responsible for triggering the disease in individuals genetically predisposed to it. Overall, what prompted researchers to look at the microbiota was the awareness that genetics plays a relatively small part in the risk of developing MS. Despite the importance of the genome, other factors also play a major role. Although environmental agents are often difficult to associate with a condition, research over the past decade has clarified that our gut is directly linked to the actions of the immune system. Clearly, the microbiota is not the only trigger of MS. Rather, it looks like these microbes could worsen or promote disease progression, pushing someone with genetic predisposition across the threshold into illness or keeping them safe. Other environmental factors likely play a part in the development and progression of the disease. The above studies have identified specific bacteria that are associated with MS, confirming that gut flora components regulate T-lymphocyte-mediated adaptive immune responses and contribute to the pro-inflammatory environment in vitro and in vivo, and could therefore be involved in triggering MS in humans. Researchers provide a possible explanation of the mechanisms. On the one hand, there is an increase in immune cells that cause inflammation. A strain of bacteria found in a large number of MS patients produces proteins similar to those found in myelin to the point that the immune system could confuse the factors that attack myelin. On the other hand, the bacterial strains found in lower numbers in MS help prevent the immune system from attacking harmless gut microbes that, without these helpful species, might overreact to gut bacteria.

These findings provide exciting new evidence that some intestinal microbes could inhibit key anti-inflammatory molecules and help trigger MS, along with other genetic and environmental factors. They also broaden our knowledge on the microbial regulation of immunity and may provide a basis for the development of microbiome-based therapies in autoimmune diseases. Unlike the genome, the microbiota is very malleable and could be relatively easily changed in adults who have MS or are susceptible to the disease. Understanding how gut bacteria alter the immune response of MS patients hence encourages the detailed search for protective and pathogenic microbial components in human MS (Berer et al., 2017; Cekanaviciute et al., 2017).

1.4 Diagnosis

Nowadays the diagnosis of MS is still based on two fundamental criteria: spatial dissemination, that is, lesions affecting different and separate CNS areas, and temporal dissemination, meaning that lesions occurring repeatedly over time.

The original Schumacher diagnostic criteria (Schumacher et al., 1965) were purely based on clinical parameters that can be summarized as follows: onset age between 10 and 50 years, objective abnormalities at the neurologic exam, dissemination in space shown by clinical evidence of damage in two or more CNS areas, dissemination in time shown by two or more relapses (each lasting ≥ 24 hours and separated by at least one month) or disability progression (slow or stepwise), signs and symptoms indicating WM damage in CNS, and no better explanation. The Schumacher criteria were based only on physical examination to determine dissemination in time and space. These were subsequently modified by the Poser Committee (Poser et al., 1983) to include evoked potentials and spinal fluid evaluations that document CNS asymptomatic damage, thereby confirming dissemination in space and time. The Poser criteria could be used to determine whether a person had possible, probable, or defined MS. The most recent McDonald criteria incorporate MRI findings for determining whether brain abnormalities meet the criteria for dissemination in time and space and simplify the diagnostic outcome to 'defined MS', 'possible MS' or 'not MS' (McDonald et al., 2001). These criteria have been criticized for being too reliant on paraclinical evidence, in particular MRI changes, and some of the controversies have been addressed in the revised version published by Polman and coworkers (2005).

As with previous diagnostic criteria, individuals must have a minimum of two attacks, affecting more than one anatomical site, but, assuming an initial presentation suggestive of MS, the second lesion does not necessarily need to be clinically expressed (**Figure 3**; Compston & Coles, 2002). According to the current diagnostic criteria of Polman et al. (2005), spatial and temporal dissemination requirements may already be met at the onset of the disease using MRI. Otherwise, if these two criteria are not met in episode of the first attack, they can be reached later by repeating MRI or with other paraclinical tools.

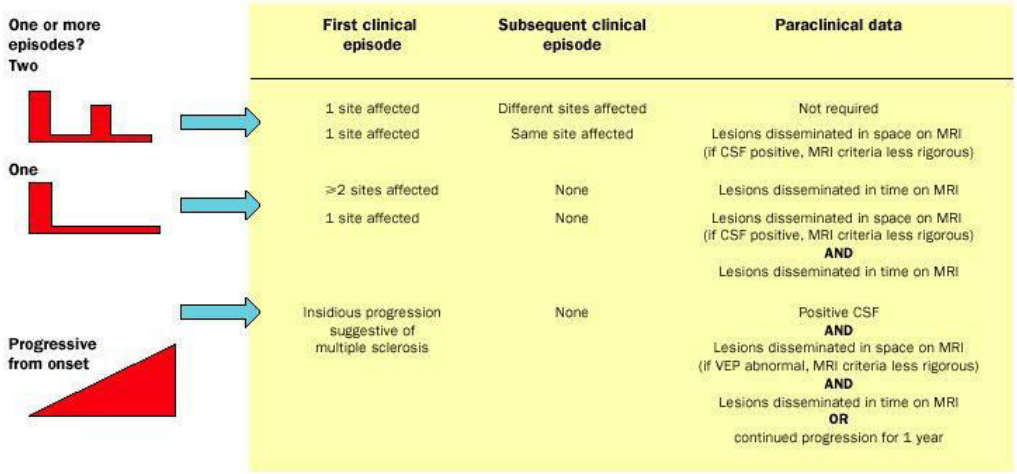

Figure 3. *Revised McDonald criteria for MS diagnosis* (Polman et al., 2005). Adapted from Compston & Coles (2002). *Lancet*, **359:**1221-31.

The principle is to establish that two or more episodes affecting separate sites within the CNS have occurred at different times – at least 30 days apart – using clinical analyses or laboratory investigations. MRI can replace one of these clinical episodes (Polman et al., 2005).

MRI criteria for dissemination in space require three of four of the following:

1. One gadolinium-enhancing (Gd+) lesion or nine hyperintense (T2-weighted) lesions.
2. One or more infratentorial lesions.
3. One or more juxtacortical lesions.
4. Three or more periventricular lesions.

A spinal cord lesion can replace some of these brain lesions. It is equivalent to a brain infratentorial lesion; an enhancing spinal cord lesion is equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with brain lesions to reach the required number of T2 lesions.

MRI criteria for dissemination in time require one of the following:

1. Detection of Gd enhancement at least 3 months after the onset of the initial clinical event.
2. Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the first clinical event.

Since a large number of diseases can mimic the WM changes seen in MS, alternative diagnoses should be considered. It is therefore important to exclude these disorders with appropriate clinical and laboratory investigations before making a diagnosis of MS. There must be no better explanation for the clinical picture.

1.4.1 Clinical investigations

In about 85% of cases, MS has a beginning with a sudden onset attack from which the majority of subjects make a full or partial recovery. This stage is referred to as a clinically isolated syndrome compatible with demyelination. A diagnosis of MS can therefore be made after one clinical attack, provided that the diagnostic criteria for dissemination in time and space are fulfilled using MRI and/or electrophysiological techniques (Rejdak, Jackson & Giovannoni, 2010).

MS clinical practice and research benefit from MRI techniques due to their high diagnostic sensitivity and rapid differential diagnosis with relatively low standard errors. In addition to the diagnosis, these advanced neuroimaging techniques are applied for their essential contribution to the identification of new active demyelinating lesions and longitudinal follow-up of the patient (Filippi, Rocca & Comi, 2003). Demyelinating lesions exhibit different features based on the scanning sequence used. T2-weighted scans show circles-like bright signal abnormalities in the WM of CNS, in which demyelinating plaques are typically seen as T2-hypertense lesions, surrounded by edema indicating an important inflammatory activity. In the FLAIR (fluid-attenuated inversion recovery) T2-weighted scans, in which the CSF signal is suppressed, the demyelinating lesions appear hyperintense. Especially in the axial section images, it is possible to appreciate small lesions arranged in the deep WM, often affecting the periventricular areas and the corpus callosum (**Figure 4A**; Noseworthy et al., 2000), or spinal cord (**Figure 4B**; Compston & Coles, 2002). FLAIR sequences are also more sensitive in detecting juxtacortical and periventricular lesions, while T2 sequences in identifying infratentorial lesions. In T1-weighed sequences, the same lesion is seen as dark, i.e. an old, scarring, gliotic plaque. The so-called ‘black holes’ are demyelinating lesions that have come to an atrophic evolution and exhibit a hypointense signal on MRI scan (**Figure 4C**; Noseworthy et al.,

2000). Following intravenous administration of gadolinium-based contrast agent, BBB breakdown areas are identified, which appear as hyperintensity regions on T1-weighted scan (**Figure 4D**; Noseworthy et al., 2000).

CSF examination is widely used to highlight an inflammatory state within the CNS, characterized by an increase in cells and proteins, thereby helping to rule out other inflammatory conditions that may mimic MS. Approximately 90% of MS cases exhibit an increase in IgG class immunoglobulins, particularly the so-called oligoclonal bands (**Figure 4E**, left pane; Compston & Coles, 2002). The detection of intrathecal oligoclonal IgG bands (OCBs) in the CSF is an invariable feature of MS that suggests an inflammatory process in the CNS and may be helpful for diagnosing the disease. According to revised McDonald criteria (2005), if there is the case of a single attack and clinical evidence of a single lesion, the presence of two T2 MRI lesions and OCBs in the CSF is sufficient to reach the demonstration of spatial dissemination and then formulate the diagnosis of 'possible MS'. If there are two attacks and clinical evidence of a single lesion, i.e. temporal dissemination, the presence of OCBs and the increase in IgG index complies with the spatial dissemination criterion and allows the diagnosis of 'defined MS'. However, if the CSF analysis does not show the local synthesis of OCBs it should make one reassess the case or at least consider alternative diagnoses (Polman et al., 2005).

Evoked potentials have a smaller but complementary diagnostic value, being able to demonstrate CNS suffering and subclinical lesions. Conduction times of nerve impulses are often abnormal in MS and are useful diagnostically as they are able to detect clinically silent foci of demyelination in specific sensory and motor pathways. The evaluation of latencies of visual, auditory and somatosensory evoked potentials, which may be delayed in MS, can also provide support for the spatial dissemination criterion (**Figure 4E**, right pane; Compston & Coles, 2002). They are also useful if they show clear evidence of delay in central conduction time, a pathognomonic feature which is not 100% specific of demyelinating disease (Gronseth & Ashman, 2000).

Many diseases may simulate MS, including viral infections, syphilis, borreliosis, vasculitis, brain lymphoma, other autoimmune diseases, and so on. It should be remembered that none of these tools has an absolute diagnostic value.

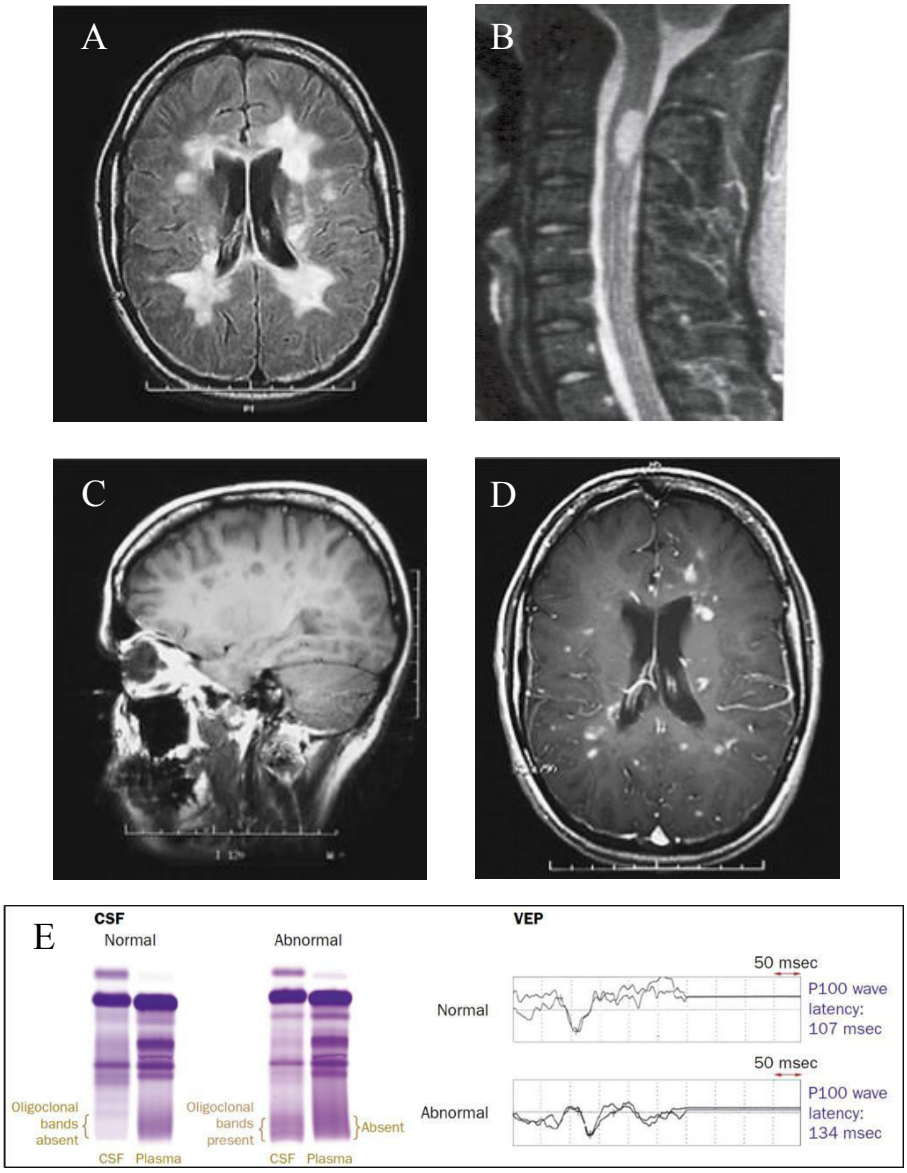

Figure 4. *Clinical investigations for MS diagnosis*. **(A)** An axial FLAIR T_2-weighted MRI scan of MS brain shows multiple ovoid hyperintense lesions in the periventricular WM. **(B)** A cervical spinal cord lesion. **(C)** A parasagittal T1-weighted MRI scan shows multiple regions in which the signal is diminished (referred to as "black holes" corresponding to chronic lesions) in the periventricular WM and corpus callosum. **(D)** After Gd administration, many of the lesions demonstrate ring or peripheral enhancement, indicating the breakdown of the BBB. **(E)** CSF protein electrophoresis highlights oligoclonal IgG bands in more than 90% of MS cases. Latency of evoked visual potentials (VEP) is typically delayed in MS patients, reflecting the specific effect of demyelination on saltatory conduction. Adapted from Noseworthy et al. (2000). *NEJM*, **343**(13):938-52; Compston & Coles (2002). *Lancet*, **359**(9313):1221-31.

1.4.2 Neurological signs and symptoms

MS is characterized by a wide range of signs and symptoms that depend on the lesion site. As a result, patients may suffer from different problems, which have great variability and frequency. The most affected sites include the brain, optic nerve, spinal cord, cranial nerves, brainstem, and cerebellum. The consequence of multifocal demyelination is the heterogeneity of MS typical signs: motor, sensory, visual, cerebellar, intestinal, urinary, sexual, and cognitive as well as numerous paroxysmal symptoms. Some of these are quite common, others are rare or appear many years after the disease onset. Anyway, not all the symptoms described are necessarily experienced during the course of the disease (Compston & Coles, 2002; Noseworthy et al., 2000).

Motor disorders include limb weakness (hyposthenia), gait ataxia, impaired ability to control movements in a coordinated fashion (limb dysmetria), and loss of strength. The latter may hit one or more limbs and the deficit may be partial (paresis) in the milder cases or total (plegia) in more serious cases, leading to the total abolition of movement. In addition to loss of strength, an increase in muscle tone, i.e. a rise in resistance to passive movements, may occur until it reaches a severe degree of spasticity.

Lesions in sensory pathways include numbness, sensation of pricking, tingling, or tickling (paresthesia) in the limbs and trunk, and reduced sensitivity (hypoesthesia), which can lead to decreased sense of touch, temperature, vibration, or pain.

Paroxysmal disorders that cause shock-like intermittent pains may also occur, due to sensory pathways injury, muscle contractures or postural abnormalities. The Lhermitte's sign, following a cervical cord lesion, consists of electric-like sensations shooting down the back and limbs when the neck is flexed. Trigeminal neuralgia is a disorder of the fifth cranial nerve that causes episodes of sharp, stabbing pain in the cheek, lips, gums, or chin on one side of the face.

Visual disturbances are among the most common symptoms reported and may be due to two main causes, which are lesions of the optic nerve or of nerve pathways controlling eye movements. In the first case, the optic (or retrobulbar) neuritis occurs, which is often associated with MS onset (25%) and is characterized by an acute reduction in unilateral *visus*, frequently related with orbit pain. In the second case, nerve path lesions in the brainstem can cause alterations in eye movements, such as double vision

(diplopia), oscillopsia and nystagmus. Oscillopsia is characterized by abnormal jerky movements of the eyes creating a subjective sensation of stationary objects swaying back and forth. Nystagmus is an involuntary, rapid and repetitive movement of the eyes — either horizontal (side-to-side), vertical (up and down) or rotary (in a circle). The Uhthoff's sign is a transient temperature-dependent numbness, weakness, or loss of vision. The temporary decrease in vision, double vision, or nystagmus occurs when body temperature rises, e.g. following a hot shower, exercise, or fever. Nystagmus and oscillopsia are also observed in vestibular tract lesions, along with vertigo, nausea, and equilibrium disorders.

Cerebellar or coordination disorders cause tremors, unsteadiness and staggering gait, characterized by a broad-based gait (ataxia). The movement loses its fluidity, becoming the characteristic intentional tremor, just as the flow of language slows down.

Fatigue is the typical non-specific symptom of MS, which involves a subjective feeling of physical or mental energy loss interfering with daily routine activities, occupational and social life. Cognitive deficits are common since the early stages of the disease and mainly involve impaired attention, episodic and working memory, and processing speed. Emotional disturbances are quite possible. The disease modifies how individuals perceive their body shape (dysmorphism), which can be a source of frustration and bad feelings. Anxiety, depression or insomnia can also arise due to functional constraints, unpredictability of disease course, or fear of worsening health. As soon as the disease gets worse, tonic spasms, progressive quadriparesis, intestinal and swallowing (dysphagia) disorders, bladder and sexual dysfunction may occur. Conversely, cortical signs (early dementia, aphasia, seizures) are rarely seen.

MS patient disability is clinically evaluated by using the Extended Disability Status Scale (EDSS), developed by John F. Kurtzke (1983). The EDSS is a global neurological index to quantify and monitor changes in the disability level over time, estimating the degree of neurological impairment, and it is widely used in clinical trials and in the assessment of people with MS. The EDSS scale ranges from 0 (normal neurological examination) to 10 (death due to MS) in 0.5 unit increments representing higher levels of disability, and is based on measures of impairment in eight functional systems (FS): pyramidal (weakness or difficulty moving limbs); cerebellar (ataxia, loss of coordination or tremor); brainstem (problems with speech, swallowing and

nystagmus); sensory (numbness or loss of sensations); bowel and bladder functions; visual; mental (or cognitive); other. Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (severe disability) and allows neurologists to assign a Functional System Score (FSS) in each of these. EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid, while steps 5.0 to 9.5 are defined by the impairment to walking. The scale is sometimes criticized for its reliance on walking as the main measure of disability. Although the scale takes into account the disability associated with advanced MS, most people will never achieve these scores.

1.5 Clinical course and outcomes

MS is a heterogeneous disease with a high variable clinical course. In 1996, a first classification approved by the international consensus identified four clinical patterns of MS, associated with a specific inflammatory response (**Figure 5**; Lublin & Reingold, 1996).

- Relapsing-remitting MS (RRMS): clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery; periods between relapses characterized by a lack of disease progression (Lublin & Reingold, 1996).

RRMS is characterized by alternating episodes of neurological disability (relapse) and recovery (remission). It is the most common form affecting about 85% of newly diagnosed patients, between the ages of 20 and 40 and with a female prevalence of 2:1 (Noseworthy et al., 2000). Clinical relapses are defined as episodes of transient neurological disturbances due to disease activity, which last for at least 24 hours and are not better accounted for by other clinical conditions (Leary, Porter & Thompson, 2005). Their clinical manifestations are variable, ranging from optic neuritis to motor or sensory disorders, making diagnosis challenging. This attack generally occurs one or two times per year and is followed by periods of remission, in which the neurological functionality is partially or completely recovered within weeks to months. Radiological relapse is defined as the appearance of new demyelinating lesions revealed by MRI that are

typically, but not exclusively, placed in WM in the absence of clinical symptoms (Loeb & Favale, 2003).

- Secondary-progressive MS (SPMS): initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus (Lublin & Reingold, 1996).

SPMS may be seen as a long-term outcome of RRMS. Indeed, the majority of RR patients will go onto SP disease after 10 years (Noseworthy et al., 2000). In this pathway, the inflammation is reduced, but a slow CNS atrophy occurs. The disability is acquired relentlessly, primarily affecting the motor function of lower limbs, with fewer relapses and an incomplete recovery. Patients with relapsing-SP form are more likely to have evidence of disease activity on MRI and to respond, modestly, to immunomodulatory therapies (Rejdak, Jackson & Giovannoni, 2010).

- Primary-progressive MS (PPMS): disease progression from onset with occasional plateaus and temporary minor improvements allowed (Lublin & Reingold, 1996).

PPMS is characterized by a progressive decline from disease onset and disability worsening without relapses. It is the least common form affecting approximately 10% of patients, usually around age 40 and with a similar incidence in males and females (Hauser & Oksenberg, 2006; Miller & Leary, 2007). This form has a relatively non-inflammatory pathway with a stable and poor lesion load that often occurs in the spinal cord and, less frequently, in the brain, optic nerve or cerebellum (Hauser & Oksenberg, 2006).

- Progressive-relapsing MS (PRMS): progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuous progression (Lublin & Reingold, 1996).

About 5% of PP patients experiencing acute relapses are included in this subgroup (Hauser & Oksenberg, 2006).

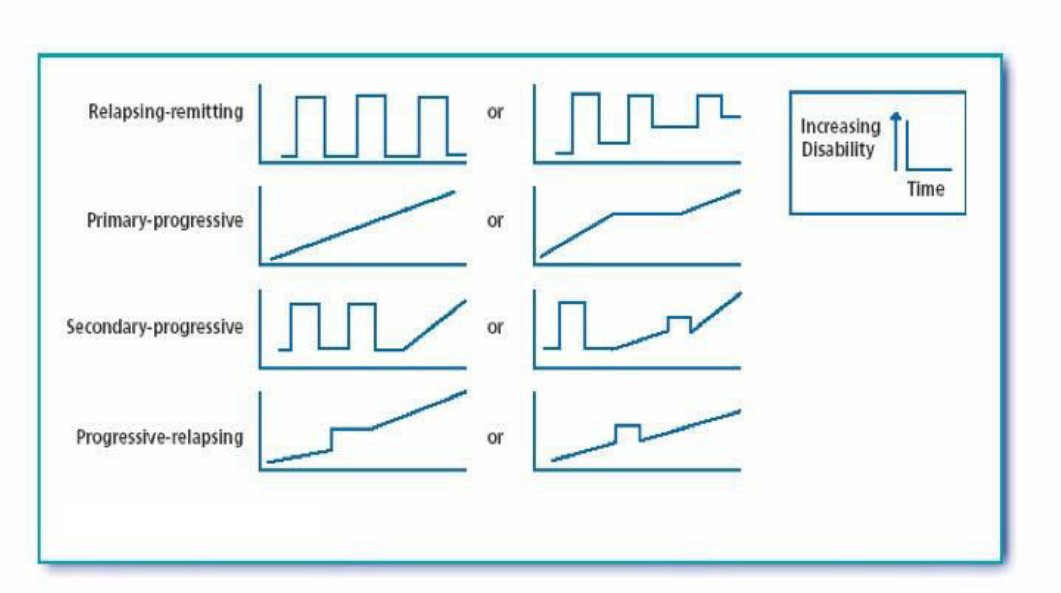

Figure 5. *The four clinical patterns of MS, based on disease progression*. Adapted from Lublin & Reingold (1996). National Multiple Sclerosis Society (USA) Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*, **46**(4):907-11.

The disease course was further complicated by the difficult to identify the early forms often preceding MS onset. The use of advanced imaging techniques and fluid biomarkers analysis in clinical practice and research has allowed the identification of two emerging phenotypes of MS. The clinically isolated syndrome (CIS) is defined by a distinct neurological event with observed demyelination, which may involve the spinal cord, brainstem, or optic nerve (Miller et al. 2005). Since CIS does not meet spatial and temporal dissemination criteria, it cannot yet be considered MS. Patients with both CIS and MRI plaques have a high risk of developing MS, but CIS may also remain an isolated episode. Otherwise, early signs of the disease could be recognized as results of radiological abnormalities in the absence of clinical manifestations, namely radiologically isolated syndrome (RIS), which often precede the MS onset. Incidental MRI findings suggesting inflammatory demyelination observed in RIS may raise the suspicion of MS, but it needs to be confirmed by clinical evidence (Lublin et al., 2014; Milo & Miller, 2014).

In 2013, a growing understanding of MS and its pathology led to a reexamination of MS disease courses (Lublin et al., 2014). The core phenotypes, relapsing-remitting and progressive disease, described in 1996 have been retained with some modifications. Newer characterizations of MS courses included a consideration of disease activity and disease progression, and a review of the terms in favor of accurate descriptions of the clinical pathways (Lublin, 2014).

Core phenotypes and modifiers

All MS forms have been sub-categorized according to disease activity, as measured by clinical relapses or CNS active lesions (the presence of new T2 or Gd+ lesions), over a specified period, preferably at least one year. Patients with progressive MS have been further differentiated between those showing signs of disability progression over a given period and those remaining stable.

CIS is now recognized as the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill the criteria of dissemination in time. RIS is no longer considered to be a part of the spectrum of MS phenotypes because of patients' lack of clinical signs and symptoms. MRI findings alone are not sufficient to establish a diagnosis of MS.

CIS is a clear-cut syndrome such as optic neuritis, brainstem/cerebellar dysfunction or partial myelitis, and is considered part of the RRMS disease spectrum. To be classified as active, a clinical or radiological event (Gd+ or new/enlarging T2 lesions) must follow the CIS. Classification as RRMS requires MRI evidence of dissemination in space, as well as Gd+ and non-enhancing T2 lesions, on a single MRI scan and/or a subsequent event. RRMS is also characterized as active or inactive within a specified time period (e.g., 6 months, 1 year). Assessments for disease activity should be conducted at least annually, but the actual time frame can be an individual decision based on routine clinical practice. Inclusion of the activity as a modifier of clinical courses has led the PRMS phenotype to be eliminated and categorized as 'PPMS with activity'.

PPMS is not considered as a separate entity but part of the spectrum of progressive disease, in which differences between phenotypes are quantitative rather than qualitative. Since the worsening of conditions proceeds at a similar rate in SPMS and PPMS, PPMS probably has no distinct pathophysiological characteristics from relapsing forms of MS

that have entered a progressive course. Traditionally, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. To date, there are no clear clinical, imaging, immunological or pathological criteria to determine the transition point when RRMS converts to SPMS.

An additional modifier of disease course is whether there is clinical evidence of disease progression, regardless of relapses, over a given period of time in patients who have a progressive course (PPMS or SPMS). Progressive disease does not progress uniformly and may remain relatively stable. The progression is determined annually by history or objective measure of change. Therefore, progressive disease has four possible sub-classifications considering the level of disability: active and with progression (e.g. individual has had an attack and is also gradually worsening); active but without progression (e.g. individual has had an attack within a previous specified timeframe, i.e. 1 or 2 years); not active but with progression (e.g. walking speed has decreased); not active and without progression (stable disease).

A patient with PPMS who has not progressed in the past year would be classified as 'not progressive PPMS'. A patient with SPMS who has gradually worsened and has Gd+ lesions on MRI would be classified as 'active and progressive SPMS'. Identification of these groups is considered important because a progressive patient with activity may respond differently to a disease-modifying therapy than a progressive patient without activity.

Terminology

The term 'worsening' has been recommended to describe patients whose disease is advancing due to frequent relapses or incomplete relapse recovery, whereas the term 'progression' should be reserved for those with progressive disease with evidence of gradual worsening over time (as opposed to worsening from a relapse).

The term 'sustained worsening' was used as a clinical trial outcome, referring to a worsening of the EDSS score that persists for a certain period (usually 3 or 6 months), and was interpreted as a measure of worsening disability. Since sustained implies a permanence that is sometimes not a feature of disease change in MS, it is therefore a potentially misleading concept. It is suggested that the term 'confirmed worsening' over

a defined period is preferably used to ‘sustained worsening’ to guide evaluation of the worsening disability. Therefore, the confirmed accumulation of disability would be defined by a worsening of EDSS that persists over x months, from the diagnostic to functional system.

It is recommended to use with caution the terms ‘benign’ and ‘malignant’ to describe disease course. Benign is not a definitive but a retrospective diagnosis and may be deceiving because MS can get worse at any time, even after long periods (e.g., 10 or 20 years) of apparent stability.

The natural course of MS is largely unpredictable. However, some factors are indicative of favorable outcomes, such as female sex, sensory or visual symptoms, and full recovery from relapses. Conversely, male sex, motor involvement, frequent relapses, and large number of brain lesions in the early stages of the disease are predictive of more severe MS progression (Brex et al., 2002).

1.6 Treatment and management

Since the causes of MS are unknown, the proposed treatments are not etiological, but are aimed at the underlying mechanisms of the disease. The main pharmacological MS targets therefore include the initial development of the pathogenic cell population inhibition, the blockage of immune cell migration into the site of inflammation and the neutralization of effector molecules produced by activated immune cells (Ghezzi & Zaffaroni, 2013).

All available therapies for MS are intended to modulate the immune system and are prevalently indicated to treat RRMS form, which is featured by active inflammation. Medications are modestly effective in RRMS in decreasing the number of attacks and in reducing the accumulation of brain lesions, which is measured using Gd enhancement on MRI (Compston & Coles, 2008). The earliest clinical presentation of RRMS is the CIS, that is, a single subacute attack suggestive of demyelination; but the patient does not fulfil the criteria for MS diagnosis (Miller et al., 2005). Treatment with interferons or glatiramer

acetate after an initial attack decreases the risk of developing clinically definite MS (Bates, 2011; Compston & Coles, 2008).

Treatment of advanced forms is more difficult. A wide range of medications has been used to try to slow down the progression of the disease, for example in SP and PR courses, with results that have been fair at best. Until recently, no effective treatment was available for progressive forms of MS, in which inflammatory episodes are rare or even not present (La Mantia et al., 2012). In particular, the treatment of PPMS is problematic as many patients do not respond to any available therapy, but the recent approval of the ocrelizumab by the European Medicines Agency (not yet in Italy) bodes well for the future treatment of this form of the disease. Several trials have been conducted to evaluate the efficacy of different drugs (i.e., beta-interferons, mitoxantrone, glatiramer acetate, or riluzole) without positive results. People with PPMS were also included in trials of azathioprine, methotrexate, intravenous immunoglobulin, cyclophosphamide, and hematopoietic stem cell transplantation (Leary & Thompson, 2005).

The primary aims of therapy are restoring function after an attack, preventing new attacks and disability. Symptomatic therapies are targeted to relapses and to a wide range of symptoms with the aim of decreasing their duration, severity and intensity. Reducing the relapse rate, preventing and slowing the progression of the disease are the goals of disease-modifying treatments. In addition to pharmacological treatments, physical therapy, neurorehabilitation and occupational therapy are important for maintaining the physical-functional-social-emotional wellbeing of all MS people (Ghezzi & Zaffaroni, 2013).

1.6.1 Acute attacks

Steroids have a prominent role in treating relapses and are the most powerful anti-inflammatory drug available to reduce Gd enhancement in acute lesions (Ghezzi & Zaffaroni, 2013).

Methylprednisolone (Urbason® and Solumedrol®). Administration of high doses (500-1000 mg/die) of intravenous corticosteroids over a period of three to seven

days is the routine therapy for acute relapses. It is usually a well-tolerated drug and has a well-established efficacy in promoting faster recovery from disability after an attack (Goodin et al., 2002; Sellebjerg et al., 2005).

Treatment can be followed by low-dose oral prednisone (Deltacortene® 60-80 mg/die). Steroids administered orally have a similar efficacy and safety profile to intravenous treatment. Major side effects include nervousness, palpitations, insomnia, stomach ache, or gastric distension (Burton et al., 2012). The consequences of severe attacks that do not respond to corticosteroids could be treated by plasmapheresis.

Plasmapheresis. This is a partially invasive procedure involving the extraction of extracorporeal plasma (water, proteins and antibodies). Usually 3 liters of plasma are removed 3 times per week until a stable improvement (less than 6 sessions) is achieved. Mild side effects include hypotension or bradycardia, transient cardiac arrhythmias, nausea, numbness, chills, and blurred vision (Compston & Coles, 2008).

1.6.2 Disease-modifying treatments

In the recent past, several disease-modifying treatments have been approved by regulatory agencies of different countries, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA). Approved drugs include: two interferons, beta-1a and beta-1b; four immunomodulators, glatiramer acetate, fingolimod, teriflunomide, and dimethyl fumarate; three monoclonal antibodies, natalizumab, alemtuzumab and daclizumab; and one immunosuppressant, mitoxantrone (Ghezzi & Zaffaroni, 2013).

These drugs are divided into two categories, namely first- and second-line treatments, depending on whether they are indicated for early forms of illness or for refractory or rapidly evolving forms. This distinction is governed by rigorous eligibility criteria established by EMA and AIFA. Currently, disease-modifying drugs used as first-line treatments for RRMS include interferons, glatiramer acetate, teriflunomide and dimethyl fumarate. As second-line treatments, fingolimod, natalizumab and mitoxantrone have been licensed for people with active MS.

Interferon beta (IFNβ)

IFNβ is the world's first officially registered drug for the treatment of RRMS. It is a glycoprotein of 166 amino acids, normally produced by the human body in very small quantities, and it is endowed with numerous modulation properties of the immune system, including the ability to antagonize the IFN-γ (Ghezzi & Zaffaroni, 2013). The IFNβ balances the expression of pro- and anti-inflammatory agents in the brain and reduces the number of inflammatory cells crossing the BBB. Indeed, it can decrease the migration of inflammatory cells in the CNS, inhibit the proliferation of T-lymphocytes and pro-inflammatory cytokines (i.e., IFN-γ), thus enhancing the production of anti-inflammatory cytokines (i.e., IL-4, IL-10). Overall, therapy with IFNβ leads to a reduction of inflammation, an increase in nerve growth factor production and, consequently, an improvement in neuronal survival (Kieseier, 2011).

There are three commercial preparations of IFNβ, one IFNβ-1b and two IFNβ-1a, which are distinguished from each other by minimal molecular-level differences: IFNβ-1a is isolated from mammalian cells, while IFNβ-1b is synthesized from bacteria by recombinant DNA technique. All three formulations are licensed for people with RRMS and an EDSS of no more than 5.5 points (i.e., walking alone for at least 500 meters). IFNβ-1b can also be prescribed for use in ambulatory patients with SP disease, with a 3 to 6.5 EDSS (i.e., walking) and with at least 2 relapses or 1 additional point at EDSS in the previous two years (Ghezzi & Zaffaroni, 2013).

In Italy, IFNβ-1a is available under the brand names:

Avonex® – 30 mg dose administered by injection into a muscle (intramuscular) once a week using a pre-filled syringe.

Rebif® – 22 and 44 mg dose given by injection under the skin (subcutaneously) three times a week with a pre-filled syringe.

Recently approved, Plegridy® is a long-acting pegylated interferon (peginterferon beta 1-a), which attaches the polyethylene glycol to interferon molecules, and is indicated for the treatment of RRMS subcutaneously. The recommended dose – 125 mg every 14 days in a pre-filled single dose pen – should be titrated, starting with 63 mg on day 1, 94 mg on day 15, and 125 mg (full dose) on day 29.

IFNβ-1b is available under the trade names:

Betaferon® and Extavia® – 8 MIU/mL dose administered by subcutaneous injection every other day – needs to be prepared by mixing ingredients before pulling into a syringe.

IFNβ-1a has demonstrated its effectiveness in decreasing the number of clinical and radiological relapses, reducing the lesion load and new active lesions on MRI, and slowing down the progression of the disease. Betaferon is the only effective interferon in reducing accumulation of disability in SPMS, measured in terms of deterioration of EDSS score (Ghezzi & Zaffaroni, 2013). The IFNβ has a few contraindications, including epilepsy, depression syndromes, thyroid dysfunction, and pregnancy. Interferons are a subclass of cytokines produced in the body during illnesses, such as influenza, to help fight infections and are responsible for many symptoms of influenza infections (fever, muscle pain, fatigue, and headache). Many patients report flu-like symptoms hours after taking IFNβ that usually improve within 24 hours; symptoms related to the temporary increase of cytokines (Compston & Coles, 2008; Walther & Hohlfeld, 1999). This reaction tends to disappear after 3 months of treatment and its symptoms can be treated with over-the-counter nonsteroidal anti-inflammatory drugs (500-1000 mg of paracetamol or 400-800 mg of ibuprofen) which reduce fever and pain. Another common transient secondary effect is a functional deterioration of the already existing symptoms of the disease. Such deterioration is similar to that produced in MS patients due to heat, fever or stress (Uhthoff's phenomenon), which usually appears within 24 hours of treatment, is more common in the initial months of treatment, and may last several days. Spasticity is a particularly sensitive symptom of worsening. IFNβ can also reduce the number of white blood cells (leukopenia), lymphocytes (lymphopenia) and neutrophils (neutropenia), as well as affect the liver function. In most cases, these effects are non-dangerous and reversible. Finally, skin reactions at the injection site are quite common side effects and may include bruising, erythema, pain, itching, irritation, swelling, and in more extreme cases cutaneous necrosis (Ghezzi & Zaffaroni, 2013; Walther & Hohlfeld, 1999).

Glatiramer acetate (GA, Copaxone®)

Previously known as copolymer-1, GA is a mixture of random polymers of four amino acids (glutamic acid, lysine, alanine, and tyrosine) which is antigenically similar to the myelin basic protein, a component of the myelin sheath of nerves with which it competes for presentation to T-cells. A further aspect of its action concerns the expression in the brain of the anti-inflammatory cytokines IL-10 and transforming growth factor β by the GA-specific cells, in addition to brain-derived neurotrophic factor, whereas they do not express IFN-γ (Arnon & Aharoni, 2004).

GA – injected subcutaneously with a pre-filled syringe at a dose of 20 mg daily, or 40 mg three times a week (preferably on the same days of the week), at least 48 hours apart – is indicated for use in RRMS up to 5 EDSS points.

Similar to interferons, GA is able to reduce the relapse rate and also has a positive effect on MRI markers of disease activity, but it cannot delay the progression of disability. Both GA formulations have no contraindications and have been approved for use during pregnancy. The most common side effects are limited to skin reactions and pain at the injection site, but inflammation of the respiratory tract, gastroenteritis, herpes, tachycardia, flushing, nervousness, anxiety, headaches and nausea may also occur (Ghezzi & Zaffaroni, 2013).

Teriflunomide (Aubagio®)

Teriflunomide is considered a selective immunosuppressant, with anti-inflammatory properties. It is a derivative of leflunomide already used in the treatment of rheumatoid and psoriatic arthritis (Ghezzi & Zaffaroni, 2013).

Teriflunomide is able to inhibit a mitochondrial enzyme involved in DNA synthesis, disrupt the interaction of T-cells with antigen presenting cell, and thus produce multiple immunomodulatory effects: inducing the synthesis of anti-inflammatory cytokines, inhibiting the expression of pro-inflammatory molecules, cell adhesion molecules and extracellular matrix metalloproteinases, and reducing the production of free radicals. The endpoint is an inhibition of replication, migration and function of activated T- and B-lymphocytes. The exact mechanism of its action is not fully understood, but it has been shown to be able to reduce the relapse rate and the progression

of disability (30%). Its effectiveness is similar to other immunomodulators, but with the great advantage of oral administration (Ghezzi & Zaffaroni, 2013; Killestein, Rudick & Polman, 2011).

The drug – a 14 mg film-coated tablet once daily – is generally well tolerated: diarrhea, nausea, paresthesia, urinary and respiratory infections, thinning hair, and increased blood concentration of liver enzymes (alanine aminotransferase) are indicated as mild side effects (Ghezzi & Zaffaroni, 2013).

Dimethyl fumarate (BG-12, Tecfidera®)

BG-12 is a second-generation ester of fumaric acid, already in use for the treatment of psoriasis. Although its mechanism of action is not entirely clear, dimethyl fumarate exhibits immunomodulatory properties, including the inhibition of pro-inflammatory cytokines and chemokines and synthesis of anti-inflammatory agents and antioxidant properties, by the induction of neuroprotective and detoxifying factors (Ghezzi & Zaffaroni, 2013).

BG-12 is an oral medication that, in the two daily doses, can reduce the annual relapse rate, as well as provide significant results on MRI parameters. The starting dose is one 120 mg capsule twice a day (days 1 to 7), and the maintenance dose is one 240 mg capsule twice a day after day 7.

Common side effects include facial or body redness, flushing, itching, gastrointestinal disorders (diarrhea, nausea and abdominal pain), and lymphopenia. The persistence of low levels of white blood cells over a long period of time may increase the risk of infections, including progressive multifocal leukoencephalopathy (PML). PML is a rare opportunistic infection with neurological progressive symptoms caused by the replication of the JC virus in the glial cells of the brain. Symptoms of PML may be similar to those of MS relapse and may include the onset or worsening of weakness on one side of the body (hemiparesis); poor coordination; alterations of sight, of thought, or of memory; or confusion or personality changes lasting more than a few days (Ghezzi & Zaffaroni, 2013; Killestein, Rudick & Polman, 2011).

Fingolimod (FTY720, Gylenia®)

Fingolimod, a sphingosine-1-phosphate receptor modulator, is the first oral drug approved for RRMS. FTY – one 0.5 mg capsule once a day – can decrease the annual relapse rate, reduce the MRI lesion load and slow the progression of the disease. For these reasons, Fingolimod has been approved as second-line drug for MS (Ghezzi & Zaffaroni, 2013; Killestein, Rudick & Polman, 2011).

FTY acts as a functional antagonist of sphingosine-1-phosphate receptors on the surface of T-lymphocytes, preventing them from leaving secondary lymphatic organs (spleen and lymph nodes). This results in a marked reduction (approximately 70%) of the amount of circulating lymphocytes, preventing their entry into the CNS, and thus ensuring a normal immune response to viruses and bacteria. FTY also act on CNS cells, inducing the synthesis of neuroprotective factors for the repair and re-myelination of the axons (Ghezzi & Zaffaroni, 2013).

Fingolimod is indicated in people with high disease activity despite IFNβ therapy, characterized by failure to respond to a complete and adequate (at least one year) therapeutic cycle with IFNβ, at least one relapse in the previous year during therapy, and presence of at least nine hyperintense T2 lesions on MRI or at least one Gd+ lesion. Otherwise, Fingolimod may be prescribed in severe and rapidly evolving RRMS, defined by two or more disabling relapses within a year, and with a significant increase in T2-related lesions compared to a recent MRI, or one or more Gd+ lesions.

FTY is usually well tolerated: the most common side effects include increased risk of infections, cough, headache, back pain, diarrhea, bradycardia, and macular edema (Ghezzi & Zaffaroni, 2013).

Natalizumab (NAT, Tysabri®)

Natalizumab was the first monoclonal antibody (MoAb) to be approved in the USA and in Europe for the treatment of RRMS.

NAT is a humanized MoAb that selectively blocks a cell adhesion molecule, α4-integrin, on the surface of circulating white blood cells. As a result, it prevents the activated T-lymphocytes from adhering to endothelial cells and overcoming the BBB,

thereby interfering with their migration into the CNS to initiate or reactivate an inflammatory response (Ghezzi & Zaffaroni, 2013).

Natalizumab – 300 mg administered by intravenous infusions every 4 weeks – has demonstrated a remarkable clinical efficacy significantly higher than any drug available so far: it decreases the annual rate of relapses (68%), the risk of progression of disability (42%), the number of T2-weighted MRI lesions (83%), and the number of Gd+ lesions (92%) (Ghezzi & Zaffaroni, 2013).

NAT is licensed as second-line monotherapy for RRMS patients who have not responded to a complete and adequate therapeutic cycle with other immunomodulatory therapies; or those with a very active disease, defined as rapidly worsening MS, even if not previously treated with immunomodulators or immunosuppressants (Ghezzi & Zaffaroni, 2013).

Common side effects include allergic reactions, hives, increased risk of infections, headache, tiredness, joint pain, nausea, and vomiting. The major adverse event, but fortunately very rare, is the PML (Ghezzi & Zaffaroni, 2013). Soon after its approval, natalizumab was withdrawn from the market after being linked to three cases of this rare but dangerous neurological condition. All 3 initial cases were taking NAT in combination with IFNβ-1a. After a safety review, the drug was returned to the market as a monotherapy for MS under a special prescription program. Since the previous use of MS treatments increases the risk of PML between 3 and 4-fold, it has been approved for human use only as monotherapy in Europe. The estimated prevalence of PML is 1.5 cases per thousand natalizumab users. Around 20% of MS patients with PML die, while most of the remaining are severely disabled (Kappos et al., 2011).

Alemtuzumab (MoAb CD52, Lemtrada®)

Used in the treatment of chronic lymphocytic leukemia, cutaneous T-cell lymphoma and T-cell lymphoma under the trade names of Campath, MabCampath and Campath-1H, alemtuzumab is probably the most powerful drug ever tested in MS (Ghezzi & Zaffaroni, 2013; Saidha, Eckstein & Calabresi, 2012).

A recombinant DNA-derived humanized MoAb directed against CD52, i.e. a glycoprotein expressed on the surface of essentially all normal and malignant B- and T-

cells, a majority of monocytes, macrophages and natural killer cells. This agent binds selectively to CD52, thus triggering a host immune response that leads to the lysis of CD52+ cells, with the saving of regulatory and memory T-cells (Ghezzi & Zaffaroni, 2013).

Compared to the highest dose of IFNβ-1a, alemtuzumab is more effective in reducing the relapse rate and EDSS score deterioration, and in increasing the rate of relapse-free patients. The power of MoAb CD52 is such that it is administered by intravenous infusion over 2 treatment courses: initial treatment course – 12 mg /die on 5 consecutive days – for 60 mg total dose and second treatment course – 12 mg /die on 3 consecutive days after 12 months – for 36 mg total dose.

This results in a prolonged reduction in white blood cells so as to be potentially dangerous for infectious diseases, which are among the most common side effects, together with infusion reactions. Important autoimmune adverse events have been reported with the thyroid (hypo- or hyperthyroidism) and platelets (thrombotic thrombocytopenic purpura) (Ghezzi & Zaffaroni, 2013).

Daclizumab (MoAb anti-Tac, Zinbryta®)

Formerly marketed to prevent acute rejection in people with kidney transplants, along with cyclosporine and corticosteroids, daclizumab was then used in 2016 to treat adults with RRMS (Lycke, 2015).

A recombinant MoAb IL-2 receptor antagonist, daclizumab binds specifically to CD25 (anti-Tac), the alpha subunit of the human IL-2 receptor expressed on the surface of activated T-cells, thereby inhibiting IL-2 binding and IL-2-mediated lymphocyte activation, a critical cellular immune response pathway. This antibody does not destroy but reduces the activity of T-lymphocytes and increases the amount of natural killer cells (Ghezzi & Zaffaroni, 2013).

Daclizumab – 150 mg injected subcutaneously once a month – has shown a 45% decrease in the annual relapse rate, a 41% drop in the proportion of patients who relapsed, and a 54% reduction in the number of new lesions (Lycke, 2015).

MoAb anti-Tac is contraindicated in people with liver impairment, including significantly elevated liver enzymes and autoimmune hepatitis. Side effects that occur

more frequently with daclizumab compared to interferon include infections (65% versus 57%), skin rashes (37% versus 19%) and liver complications (about 18% versus 12%) (Lycke, 2015).

Ocrelizumab (OCZ, Ocrevus®)

Recently approved by the EMA, but not yet by the AIFA, ocrelizumab has been licensed for the treatment of RRMS and is the first drug with proven efficacy in primary progressive forms.

Ocrelizumab is a humanized anti-CD20 MoAb and an immunosuppressive drug, like rituximab. It targets CD20 marker on B-lymphocytes, causing antibody-dependent cell-mediated cytotoxicity and, to a lesser extent, complement-dependent cytotoxicity. This MoAb selectively destroys only the B-lymphocytes, without altering the synthesis of antibodies by the plasma cells, i.e. the more mature form of B-cells, suggesting an action mechanism independent of the elimination of pathogenic antibodies. Compared to rituximab, it is better tolerable and less likely to induce PML (Ghezzi & Zaffaroni, 2013).

According to the EMA guidelines, the initial 600 mg dose is given by two different intravenous infusions: an initial 300 mg infusion followed by a second 300 mg infusion two weeks later. Subsequent doses are administered by a single 600 mg intravenous infusion, every 6 months. The most important and most frequently reported adverse drug reactions include infusion-related reactions, respiratory infections, nasopharyngitis and influenza.

Mitoxantrone (MXT, Novatrone®)

Produced by Italian pharmaceutical research, mitoxantrone is an immunosuppressant licensed for the treatment of SP and PR courses (Ghezzi & Zaffaroni, 2013).

Mitoxantrone has a high cytotoxic activity against B- and T-lymphocytes and can reduce circulating pro-inflammatory cytokines. It is very useful in reducing attacks and disability and is moderately effective in decreasing the progression of the disease and the frequency of relapses. However, it is linked to dangerous dose-dependent side effects that limit its long-term use (Martinelli Boneschi et al., 2013).

MXT – 12 mg/m^2 of body surface area given by intravenous infusion (5-15 minutes), with a three-month period – is indicated in ambulatory (not wheelchair-bound) patients with or without intermittent attacks, provided they are in the active phase of the disease, as defined by two attacks or an EDSS worsening of at least one point in 18 months (Ghezzi & Zaffaroni, 2013).

The most common side effects are: nausea, vomiting, headache, alopecia, menstrual disorders, urinary tract infections, diarrhea, and leukopenia. Mitoxantrone is generally well tolerated in prescribed doses. However, cumulative cardiac toxicity (risk of congestive cardiomyopathy) and even more bone marrow suppression (risk of acute myeloid leukemia, myelodysplastic syndrome, acute leukemia) require great caution for its use (Martinelli Boneschi et al., 2013).

Unlicensed therapies

Given the autoimmune nature of the inflammatory process of MS, there are numerous immunosuppressants among the most commonly used medications. Essentially the same products used for cancer chemotherapy, they are administered at very low doses, in order to exploit their ability to suppress any immune response (Ghezzi & Zaffaroni, 2013).

Azathioprine, methotrexate and cyclophosphamide are some of the agents that are commonly used off-label as disease-modifying treatments in MS. All immunosuppressants may cause, to a different extent, nausea, diminished counts of white blood cells, red blood cells and platelets, menstrual cycle changes, and liver dysfunction. They also require extreme caution and rigorous monitoring for their use due to long-term harmful effects (sterility, cancer risk, fetal malformations) (Ghezzi & Zaffaroni, 2013; Rejdak, Jackson & Giovannoni, 2010).

1.6.3 Symptomatic therapies

Despite the intense focus on disease-modifying treatments, symptomatic and physical therapies remain the cornerstone of the long-term management of MS. As the disease has an impact on a wide number of functional neurological systems, symptomatic therapies have the potential to significantly improve the quality of life of people suffering from the

ravages of the disease. At the same time, for each symptom there are different treatment options (**Table 1**). These should therefore be individualized depending on both the patient and the physician (Rejdak, Jackson & Giovannoni, 2010).

Symptoms	Medical treatments
Bladder	Medications can mainly be divided into treatment of bladder control and incontinence - desmopressin for nocturia - and of urinary tract infections - anticholinergic drugs such as oxybutynin and tolterodine. Non-pharmacological management includes pelvic floor muscle training, stimulation, pessaries, bladder retraining, changes in daily life habits such as clothing, use of external urine collection devices for men and incontinence pads for women; and sometimes intermittent urinary catheterization.
Bowel	Cause of bowel impairments is usually either a reduced gut motility or an impairment in neurological control of defecation. The former is commonly related to immobility or secondary effects from drugs used in the treatment of the disease. Pain or problems with defecation can be helped with a diet change that includes among other changes an increased fluid intake, oral laxatives, or suppositories and enemas.
Cognitive and emotional	Cognitive impairment is a frequent complication of MS, so a correct evaluation of the deficits and factors (i.e., medications, relapses or depression) exacerbating them is important. Regarding primary deficits, anticholinesterase drugs, such as donepezil, are considered effective in improving cognitive functions. The effectiveness of cognitive rehabilitation therapy is more controversial. Neuropsychiatric symptomatology is also common in the course of the disease and includes depression, anxiety and emotional lability, which can be treated with antidepressants and cognitive behavioral therapy. Other neuropsychiatric symptoms are euphoria and disinhibition. For those patients who have a pseudobulbar affect, characterized by uncontrollable episodes of crying and/or laughing, medications such as selective serotonin reuptake inhibitors (e.g., citalopram) and tricyclic antidepressants (e.g., amitriptyline) have been used in clinical practice.
Dysphagia and dysarthria	Dysphagia is a difficulty with eating and swallowing which may cause choking and aspiration of food or liquid into the lungs, while dysarthria is a neurological motor speech disorder characterized by poor control over the subsystems and muscles responsible for speech (articulation). A speech and language therapist may give advice on specific swallowing techniques, on adapting food consistencies and dietary intake, on techniques to improve and maintain speech production and clarity, and on alternative communication approaches. In the case of advanced dysphagia, food can be supplied by a nasogastric tube, or by a percutaneous endoscopic gastrostomy, although it is more invasive.
Fatigue	Fatigue is very common and disabling in MS, and at the same time it has a close relationship with depressive symptomatology: when depression is reduced, fatigue also tends to improve. In a similar way, other factors such as disturbed sleep, chronic pain, poor nutrition, or even some medications can contribute to fatigue. The drugs studied to treat MS-related fatigue include amantadine, 4-aminopyridine, psychostimulants

	such as pemoline, or modafinil, as well as psychological interventions of energy conservation, but the effects of all of them are negligible. Fatigue is therefore a very difficult symptom to manage for which no drugs are recommended.
Paroxysms	Epilepsy may occur in MS, presumably due to the involvement of the cerebral cortex. Standard anticonvulsants include carbamazepine, amitriptyline, gabapentin or pregabalin, topiramate, clonazepam, and diphenylhydantoin.
Pain and sensory losses	Altered sensation in the form of tingling, numbness, 'odd' feelings, and so on, are common in people with MS. Sensory losses may be associated with painful hypersensitivity and spontaneous neuralgic pain. While there are no proven treatments for sensory disturbances, the treatment of neurogenic pain is covered separately. Acute pain is mainly due to optic neuritis (with corticosteroids being the best treatment available), as well as trigeminal neuralgia, Lhermitte's sign, or dysesthesia. Subacute pain is usually secondary to the disease and can be a consequence of spending too long in the same position, urinary retention, and infected skin ulcers, amongst others. Chronic pain is very common and harder to treat as its most common cause is dysesthesia. Treatment will depend on the cause. Acute pain due to trigeminal neuralgia is usually successfully treated with anticonvulsants such as carbamazepine or phenytoin. Both Lhermitte's sign and painful dysesthesia usually respond to treatment with carbamazepine, clonazepam, or amitriptyline.
Sexual dysfunction	Male and female sexual dysfunction is common about which there should be specific enquiry. Medications include alprostadil, selective oral phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil), and psychological interventions.
Spasticity	Spasticity is characterized by increased stiffness and slowness in limb movement, the development of certain postures, an association with weakness of voluntary muscle power, and with involuntary and sometimes painful spasms of limbs. Physiotherapy can help to reduce spasticity and avoid the development of contractures with techniques such as passive stretching. Medications include baclofen, dantrolene, diazepam, tizanidine, gabapentin, and cannabinoids. In more complicated cases, intrathecal injections of baclofen or surgical tenotomy can be applied. Cannabinoid derivatives such as Sativex have been approved for the management of spasticity in MS in several countries and recently in Italy. This medication has shown long-term safety and efficacy.
Vision	Different drugs as well as optic compensatory systems and prisms can be used to improve the symptoms of nystagmus or diplopia (double vision). Surgery can also be used in some cases.
Walking	A novelty in the treatment of motor disorders is fampridrine, that is, a broad-spectrum potassium channel blocker to treat walking difficulties in MS. It has been shown to increase walking speed, although its high cost limits its usage.

Table 1. *Symptomatic therapies in MS*. Adapted from The National Collaborating Centre for Chronic Conditions (UK) (2004). *Multiple sclerosis: National clinical guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians.

1.6.4 Rehabilitation

Disease-modifying treatments only reduce the progression rate of the MS, but do not stop it. As the disease progresses, symptoms and functional deficits tend to increase, resulting in a range of progressive impairments and disabilities. Management of these deficits is therefore paramount.

Rehabilitation deals with the consequences of illness on the autonomy of individuals due to disorders of movement, swallowing, communication, cognitive functions, and psychological repercussions on the individual and surrounding environment. In accordance with the Italian Ministry of Health, rehabilitation is therefore a process of problem solving and education, during which a person reaches the highest possible level of personal and social life, with the least possible restrictions on his/her operative choices (Ghezzi & Zaffaroni, 2013).

Based on a clinical assessment of the person's needs, an 'individualized rehabilitation project' is developed to summarize the goals to be achieved and the activities of the various professionals (i.e., physiotherapist, occupational therapist, speech therapist, neuropsychologist, social workers and nurses). As successful rehabilitation is ensured only by a multidisciplinary approach, each operator defines a precise therapeutic program characterized by the frequency, intensity, duration, and type of rehabilitation necessary to achieve the intended outcome. Rehabilitation aims to maximize the independence of individuals, reduce disability, prevent the onset of complications, through a tailor-made rehabilitation project for people with MS. The rehabilitation team works with a person's overall care. It is a learning process for the patient and the family environment of all the motor, psychological and adaptive resources. These are aimed at improving autonomy, to be understood as decision-making and self-determination, and quality of life (Ghezzi & Zaffaroni, 2013).

Although there is currently no evidence of a more effective rehabilitation technique than the others, it is necessary to overcome the dogma that rehabilitation has no effect. Rehabilitation is indicated at the beginning of the disease as well as in chronic-progressive stages, provided that the patient's perception of discomfort occurs with his/her worsening conditions (Ghezzi & Zaffaroni, 2013).

Physical therapy

Symptoms of MS that can be improved by physical therapy and medications include fatigue, spasticity, depression, bladder dysfunction, and neurological symptoms. Physical therapists can show strengthening exercises and ways to stretch, making day-to-day activities easier and reducing fatigue while muscle strength raises as flexibility increases. As aforementioned, medications can help tiredness, pain, muscle tightness (spasticity), neuropsychiatric and neurological symptoms, while for others the efficacy of treatments is still very limited (Kesselring & Beer, 2005).

Physical therapy can help to control spasticity and damage to the associated articular and muscular apparatus. It can improve the respiratory performance, the quality of movement disturbed by ataxia or sensitivity disorders, and can reduce hyposthenia and balance disorders. Stress resistance through aerobic training, day-to-day fatigue management, energy saving strategies, correct postural positions to reduce pain, auxiliary and environmental adaptations can be learned. It is also possible to reduce swallowing, articulation and communication, urinary, fecal, and sexual disorders (Ghezzi & Zaffaroni, 2013).

Medications in association with physical therapy can contain the consequences of disease relapse: combining intravenous cortisone therapy with neuromuscular rehabilitation treatment immediately facilitates recovery of the damaged function due to relapse. Both medical treatments and neurorehabilitation have shown to ease the burden of some symptoms, even though none influences the disease progression (Ghezzi & Zaffaroni, 2013; Kesselring & Beer, 2005).

With regards to well-being, physical therapy focused on gait training can be vital to maximizing MS patient participation via reduction of fatigue during walking and activities of daily living (ADLs) (Sacco et al., 2011). Most gait training is performed over-ground (i.e., in a gym room or outside on uneven ground), on treadmills or, less commonly, using robotic-assisted devices. Robotic-assisted body weight-supported treadmill training may be an effective therapeutic option in MS patients with severe walking impairments. In contrast, over-ground gait training may be more effective in improving gait speed in MS patients with less severe impairments (Vaney et al., 2012). Equine-assisted therapies such as therapeutic horseback riding and hippotherapy are

additional treatments that can positively influence gait, balance and quality of life in people with MS (Bronson et al., 2010). Depending on the person, activities may include resistance training, kinesitherapy, walking, swimming, yoga, tai chi, and others. Determining an appropriate and safe exercise program is challenging and must be carefully individualized for each person, making sure to consider all the contraindications and precautions (O'Sullivan, 2007).

An elevated core temperature, leading to increased symptom presentation, has been noted during exercise, due to variations in circadian body temperature throughout the day, and due to heat exposure including warm temperatures, hot showers, sun bathing, and so on. Care should be taken not to overheat a person with MS during exercise. The interaction between an elevated core temperature and the pathological demyelination can cause a transient nerve conduction block that leads to a temporarily impaired physical and cognitive function. These effects translate into a reduction in patient safety and performance of ADLs, but viable prevention strategies exist. Cooling measures are effective in allowing a greater degree of physical exercise: cold showers, cold water limb immersion, applying ice packs, and drinking cold beverages as well as behavioral strategies, such as performing outdoor physical activity when temperatures are cooler, and so on, they allow to minimize heat exposure (Davis et al., 2010).

As far as rehabilitation time is concerned, it should be prolonged as the major evidence relates to low-intensity and long-term rehabilitation programs. As its benefits deteriorate progressively over time, it would be desirable for patients, if necessary with trained caregivers, to continue the exercise program in their own home to maintain long-term results. In fact, the caregiver training, education of the patient to have a positive view of rehabilitation, and adequate monitoring and re-evaluation over time by the physician are of great importance.

Rehabilitation limits relate to tremor of any origin, reduced or lost sensitivity, painful sensory disturbances, and structural damage (e.g., muscle-tendon retraction and joint rigidity). Fortunately, each of these situations has valid pharmacological or surgical responses (Ghezzi & Zaffaroni, 2013).

Neurorehabilitation

Although studies on rehabilitation in MS are not conclusive, its overall effectiveness, when conducted by a team of specialists, has been clearly demonstrated in other diseases such as stroke (Stroke Unit Trialists Collaboration, 2007) or head trauma (Turner-Stokes et al., 2015). As for any patient with neurologic deficits, a multidisciplinary approach is key to limiting and overcoming disability.

Particular difficulties in specifying a 'core team' can arise because people with MS may need help from almost any health professional or services at some point: neurologists are mainly involved in the MS diagnosis and ongoing management, and any exacerbations; the comprehensive rehabilitation process is generally managed by physiatrists. Allied treatments such as physiotherapy, speech and language therapy, or occupational therapy can also help to handle some symptoms and maintain quality of life; treatment of neuropsychiatric symptoms, including emotional distress and clinical depression, should involve mental health professionals, such as psychologists and psychiatrists, while neuropsychologists can help to evaluate and manage cognitive deficits (The National Collaborating Centre for Chronic Conditions, 2004).

Multidisciplinary approaches have been shown to be effective in increasing activity and participation levels in MS patients (Khan et al., 2008). It is difficult to be specific about which types of rehabilitation will be most beneficial, because therapies are tailored to meet the individual's specific needs. Due to the paucity of randomized controlled studies, there are limited data of the overall efficacy of individual therapy disciplines, although there is good evidence that specific approaches, such as physical exercise (Gallien et al., 2007), psychological therapies, particularly cognitive behavioral approaches (Thomas et al., 2006), and energy conservation education (Mathiowetz, Matuska & Murphy, 2001) are effective. For patients, the opportunity to continue their work, and then try to maintain their economic status, is a primary goal in the management of the disease. Feeling still active, engaging and useful to themselves and to their families is of great importance for the general welfare and quality of life of people with MS (Ghezzi & Zaffaroni, 2013; Steultjens et al., 2005).

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CHAPTER II
Neuropsychology of MS

> *There is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality. The dominant feeling in the patients appears to be an almost stupid indifference in reference to all things. It is not rare to see them give way to foolish laughter for no cause, and sometimes, on the contrary, melt into tears without reason. Nor is it rare, amid this state of mental depression, to find psychic disorders arise which assume one or other of the classic forms of mental alienation.*[1]

2.1 A "multiple disconnection syndrome"

As highlighted in the previous chapter, MS is one of the most common neurological diseases with an early onset in young adult life and a wide variety of symptomatic, personal and social sequels. From a cognitive point of view, numerous descriptions of MS-associated mental changes were already given in the 19th century (Charcot, 1868, 1877; Seiffer, 1905).

So far, many studies are comprehensive enough to provide data about the frequency and pattern of cognitive dysfunction, indicating that the most frequently impaired domains relate to memory, attention, information processing speed, abstract/conceptual reasoning, and visuospatial skills. While primary language, implicit and immediate memory, and verbal intelligence appear to be unaffected, the core deficit

[1] Charcot, J.M. (1877). Disseminated sclerosis: Its symptomatology. In G. Sigerson (Trans.), *Lectures on diseases of the nervous system delivered at the Salpêtrière* (v.1, pp. 194-195). London, UK: The New Sydenham Society.

has to do with some salient aspects of working memory (Rao et al., 1991a). The combination of the newest neuropsychological methods and brain-imaging techniques has brought unprecedented advances in understanding the nature and development of cognitive disorders and their relationship with structural brain-involvement.

Not so long ago, one of the most interesting questions that clinicians and researchers focused on was whether the neuropsychological performance of MS patients resembles the cognitive profile of people with cortical or subcortical dementia. Several researchers initially pointed out that the cognitive impairment observed in MS is generally consistent with a pattern of subcortical dementia (Beatty et al., 1990; Caltagirone et al., 1991; Filley et al., 1989). In their study, Filley and colleagues (1989) compared individuals with chronic-progressive MS and Alzheimer's disease (AD), as a prototype of cortical dementia, on 44 cognitive and psychomotor variables, and both groups were classified as demented. The AD group had a homogeneous intellectual decline, performing worst in all tests except for those that required psychomotor effort. The MS group had remarkable differences between verbal and performance measures, indicating a high impact on motor-speed disability rather than a genuine dementia profile. Subcortical dementias have been described as having a clinical resemblance to neurobehavioral dysfunctions, appearing after a frontal lobe injury, associated with emotional and personality changes, memory disorders, and cognitive inflexibility (Calabrese & Penner, 2007). Similar patterns, indicating frontal dysfunction, have also been reported in people with MS (Rao et al., 1991a). In a series of studies, neuropsychological functions of MS patients with different disease courses were investigated, showing impressive deficits in the symbol-digit-modalities-test, verbal fluency, and anterograde and remote memory measures (Beatty et al., 1988, 1989; Beatty & Monson, 1991a, 1991b). Authors assumed this pattern of disturbance, that is, memory dysfunction and slowing processing speed, to parallel the findings in patients with subcortical dementia.

When examining those memory functions supposed to be independent of conscious memory (e.g., skill memory and priming), the picture becomes less clear. At this level of information processing, people with MS are neither comparable to individuals with subcortical pathology nor with a typical cortical profile. Using implicit learning paradigms, it was found that patients with Huntington's disease (HD) failed to

acquire certain motor skills but performed lexical activities (Heindel, Butters & Salmon, 1988); in contrast, AD patients were able to learn motor tasks but showed defective priming (Salmon et al., 1988). In their study, Beatty et al. (1990) demonstrated that MS individuals fall between this double dissociation. Since the patients performed poorly on the explicit memory test, while their performance on implicit learning measures was normal for both skill learning and priming, the authors assumed that the performance of MS patients was qualitatively similar to that of amnesics, but stood in contrast to that of HD or AD patients. Consequently, Beatty and coworkers (1990) concluded that the pattern of cognitive dysfunction in MS appears to be unique and does not remark either subcortical or cortical dementia.

In short, the MS-related cognitive impairment pattern was initially labeled as subcortical dementia, in which processing speed, memory and executive functions are affected, and a profound motor and cognitive slowing is observed. Unlike cortical dementia in which aphasia, apraxia, and agnosia are the typical symptomatic triad, the clinical presentation of subcortical pathologies is characterized by mood, psychiatric and personality disorders, and cognitive inflexibility. Finally, instead of a diffuse cortical atrophy, subcortical lesions also occur in deep GM, brain stem and cerebellum. However, the high variability of lesions in MS leads to widespread heterogeneity in clinical presentations suggesting that the disease should be classified as a separate syndrome (DeLuca et al., 2015). Taking into consideration all discussed topics, several problems in categorizing the neuropsychological deficiency pattern of MS individuals are encountered. Firstly, the term subcortical dementia *per se* embraces several etiopathologically different conditions on the behavioral level and implies a neuroanatomical distinction from cortical pathologies, which is quite inaccurate, given the multiple subcortical-cortical interconnectivity (Albert, Feldman & Willis, 1974). Secondly, cognitive deficits in MS are quite variable as they depend highly on the disease dynamics and appear to be caused by manifold interruptions of different interactive fiber systems. The term dementia implies a global loss of intellectual functions and would therefore only be suitable for a very small number of patients with MS, since the residual or non-influenced functions are not as depleted as in dementia (Calabrese & Penner, 2007). As previously discussed, both GM and WM damages contribute to mental dysfunction (Sanfilipo et al., 2006), and MS-associated lesions mainly involve subcortical

periventricular fiber systems, hindering the distal flow of cortical cholinergic pathways, which is an evidence of subcortico-cortical involvement in MS (Selden et al., 1998). Calabrese and Penner (2007) have hence defined MS as "multiple disconnection syndrome", indicating this particular condition that really stands between cortical and subcortical pathologies.

2.2 Cognitive impairment in MS

Since the 1980s, cognitive dysfunction is indicated as a common concomitant of MS, with prevalence rates ranging from 40% to 70% at both the earlier and later stages of the disease (Beatty et al., 1989; Benedict et al., 2006a; Bobholz & Rao, 2003). Among the areas of cognition, processing speed and memory seem to be the most affected, while those usually spared include simple attention, verbal comprehension and naming, and general intelligence. Overt dementia is rare in MS. The depletion of cognitive domains such as memory, attention, mental processing speed, executive and visuospatial functions may occur from onset of the disease and tends to get worse over time (Rao et al., 1991a).

Cognitive deficits may not be immediately apparent to the clinician, except through a targeted neuropsychological assessment. In addition, patients tend to underestimate such difficulties, simply attributing them to 'mental fatigue'. The cognitive impairment that occurs initially in MS does not appear as a global decline in intellectual abilities, but rather as a set of discrete deficits related to specific cognitive domains, and is characterized, especially in the early stages, by a wide variability among patients. Some studies have stressed the possible role of fatigue and depression in the deterioration of these cognitive domains. It has been shown that depression can contribute to a slowdown in processing information and that fatigue requires a greater effort to record this information. Such difficulties, albeit their wide variability, seem to depend on a cortico-subcortical disconnection between frontal and temporo-parietal regions (Chiaravalloti & DeLuca, 2008).

Cognitive dysfunction is closely associated with functional status in MS. Such changes in the patients' personal, occupational, and social lives have a deleterious impact on their quality of life, resulting in significant functional impairments at work and at

home, sometimes despite minimal physical disability (Lynch, Parmenter & Denney, 2005; Patti, 2009). For this reason, developing therapeutic measures to alleviate such deficits should take precedence in MS research. The potential for individuals to improve their own cognitive brain health by habitually exercising high-order mental strategies is intriguing and is beginning to be widely explored. As a matter of fact, it has been demonstrated that complex mental activity induces improvements in cognition and brain function, but it is not yet clear to what extent the brain is capable of such plasticity (Chapman et al., 2013). Overall, the conflicting findings about the effectiveness of the various cognitive rehabilitation techniques do not allow to draw definite conclusions about their effect on cognition, mood, quality of life, fatigue, and self-efficacy. The lack of conclusive evidence in these studies may be due to heterogeneous rehabilitative approaches, methodological weaknesses, diversity in the targeted cognitive domain and treated disease subtypes. Despite these gaps, a recent systematic review has reported that most of the cognitive rehabilitation studies in MS have shown some significant benefits of these treatments (Sandroff, Schwartz & DeLuca, 2016).

Cognitive rehabilitation aims to reduce cognitive deficits, improve patient awareness and ability to account for their cognitive impairment in daily life, and ultimately promote neurobiological changes. It has been shown to be effective in ameliorating functional domains, motor and cognitive, suggesting that remediation or compensation can also occur in damaged brain structures. Neurorehabilitation is able to enhance neuroplasticity, that is, the intrinsic property of the CNS to structurally and functionally adapt itself in response to external stimuli, environmental changes, or injuries. While in healthy individuals the plasticity represents the basis of brain development, learning and memory, in the context of MS this term encompasses molecular, synaptic, cellular events and even reorganization of the brain cortex or fibers that result in recovery of function after an acute or chronic damage (Prosperini et al., 2015). The first cognitive rehabilitation programs designed for MS focused on improving communication skills, attention and memory. Although mixed effects on the benefits of these programs are reported, most of the studies that showed successful cognitive rehabilitation before 2008 involved learning- and memory-based interventions (O'Brien et al., 2008), but recently the focus has shifted to other domains, such as executive functions, processing speed and attention, as these are the cognitive functions that have

shown to be more affected by MS (Mitolo et al., 2015). Advanced MRI techniques provide a powerful tool for investigating functional and structural brain changes related to recovery of function. Recently, it has been demonstrated that rapid-onset plasticity and functionally relevant chronic reorganization processes are preserved even in the most advanced stage of the disease and that these phenomena are considerably important for the maintenance of motor and cognitive functions (Pantano, Mainero & Caramia, 2006; Tomassini et al., 2012). In most cases, the rehabilitation program is based on computer-assisted/video-game exercises performed in either an outpatient or home setting. Despite their heterogeneity, these studies describe changes in WM microarchitecture, in task-related activation, and/or in functional connectivity following both task-oriented and selective training. When explored, a significant correlation between improved function and MRI-detected brain changes is often found, supporting the hypothesis that training-induced brain plasticity is specifically linked to the trained domain (Prosperini et al., 2015). These findings are consistent with the assumption that neuroplasticity can be enhanced by rehabilitation. So far, only a few studies have analyzed the mechanisms of rehabilitation-induced neuroplasticity, providing fragmented and incomplete data. Despite this, rehabilitation is recognized to have a key role in the management of patients with MS.

2.2.1 Cognitive deficits and management

2.2.1.1 Memory

Memory disturbances appear to be the most frequent cognitive dysfunction in MS, with a prevalence ranging from 40% to 60% (Amato, Zipoli & Portaccio, 2006; Guimarães & Sá, 2012). While short-term memory is the capacity for holding, but not manipulating, a small amount of information for a short period of time, long-term memory refers to learning and storing an indefinite amount of new information over an extended, potentially unlimited time. The distinctive feature of the latter is the mental capacity of retaining and reviving facts, events, impressions, or of recalling or recognizing previous experiences (Lezak, Howieson & Loring, 2004).

The first data were published in the late 1980s and included groups of patients with different disease courses, reporting disturbances in short-term memory and delayed recall for both verbal and visual information, which led to the conclusion that memory dysfunction was a core deficit of MS (Anzola et al., 1990; Rao, 1990; Ron, 1986). Most of these studies found an impairment in memory span as well as in performing more complex tasks such as supraspan. Verbal memory measures – the story recall and selective reminding task – seem to be affected too, as over time the patients recall less details of the tale and fewer items of the word list from their long-term storage than healthy subjects (Beatty & Monson, 1991b; Rao et al., 1991a; Ron, 1986; Swirsky-Sacchetti et al., 1992). The same deficits of verbal memory were also observed in visuospatial tasks. Since the recognition is usually less impaired than the recall, it was previously hypothesized that the root cause of the deficit was retrieval rather than encoding or storage processes (Beatty & Monson, 1991b; Caine et al., 1986; Rao, 1990). Later on, another interesting explanation for memory problems concerned the deficit in the initial learning of information. By using MRI brain atrophy measures, DeLuca and coworkers (2013) demonstrated that memory deficits in MS were the result of inefficient learning across initial acquisition trials. In their study, the reduction of the third ventricle width, used as an atrophy measure, was negatively associated with both initial learning and delayed retrieval. However, the link between brain atrophy and lower retrieval disappeared when controlling for initial learning. In addition, the relationship between MS-related atrophy and subsequent retrieval was mediated primarily through initial learning, thereby supporting the core learning-deficit hypothesis of memory impairment in MS. According to this hypothesis, people with MS need more repetitions to reach the predetermined learning criterion, but once the information has been acquired, the recall is at the same level of normal controls. This deficit would be the result of faulty high-order mental processes, such as decision-making, processing speed, and executive functions (DeLuca, Barbieri-Berger & Johnson, 1994; DeLuca et al., 1998). Since MS is a demyelinating disease, resulting in slowed transmission or loss of information along the affected axons, the impairment is not related to pure memory processes, but to the frontal lobe functioning and mental slowdown (Calabresi, 2011; Smith & McDonald, 1999).

Some interesting investigations, using ‘frontal dysfunction’ measures, have revealed memory deficits for the temporal order, metamemory functions and cognitive

flexibility in MS, suggesting that this impairment was the result of damage to the temporal lobe or diencephalic memory system, and front-striatal circuit (Beatty & Monson, 1991a, 1991b; Rao et al., 1987). In the study by Grafman et al. (1991) using various measures of automatic and controlled memory processes, MS patients showed disturbances in tasks requiring effortful control operations (free and cued recall), but not in tasks demanding automatic processing (monitoring frequency and modality). The authors explained these findings suggesting that, since automatic processing requiring semantic activation is unaffected, the deficit would be in processing information at the level of articulatory loop (Baddeley, 1992). In other words, the verbal information processing within the working memory could be compromised, thus causing a deficit in recovering and rapidly processing verbal information. As discussed before, cognitive dysfunctions in MS seem to be different from those seen in subcortical or cortical dementia and therefore may better be explained on the basis of multiple disconnections (Calabrese & Penner, 2007).

In conclusion, memory appears to be one of the most frequently disturbed cognitive functions in MS. The impairment concerns learning strategies involving an inefficient recovery from short- and long-term memory and verbal working memory, while the capacity of recognition and implicit learning seems to be relatively undisturbed. In the early stage of MS, verbal episodic memory deficits appear to primarily affect information retrieval, whereas as the disability progresses they are probably related to encoding (Grzegorski & Losy, 2017). All these impairments can occur regardless of physical disability and can vary substantially among patients due to high-order process deficits, which makes difficult their identification and recognition.

Rehabilitation

Although not part of a structured treatment protocol, specific memory-enhancing techniques, such as self-generating and spacing effects, have been shown to significantly improve learning and memory in people with MS (Goverover et al., 2009). The modified Story Memory Technique (mSMT) is a well-validated imagery- and context-based memory retraining program, designed to ameliorate deficits in new learning and memory abilities in MS. Through a 10-session standardized treatment protocol, the mSMT trains individuals to use visualization and context to learn new information, leading to significant improvements observed on neuropsychological testing and self-reports of

memory in daily life when compared to a placebo-control group (Chiaravalloti et al., 2005, 2012, 2013).

Among the newer rehabilitative interventions that examined neuroimaging as an outcome measure, a double-blind, placebo controlled, randomized controlled trial (RCT) by Chiaravallotti et al. (2012) explored changes in brain activation during the execution of a word learning and recognition task after a behavioral memory intervention (mSMT). This study was the first to demonstrate a significant change in cerebral activation in the frontal and temporal regions and in the cerebellum, through cognitive rehabilitation. There was also a significant correlation between improved memory performance and increased activation of the right middle frontal gyrus, which is known to be associated with visual and context-dependent learning. The further contribution of the same research group showed that this activation pattern was maintained six months post-treatment (Dobryakova et al., 2014) and that mSMT training led to increased functional connectivity within memory networks as compared to placebo-controls (Leavitt et al., 2014a). Thus, the mSMT induces not only improvements in learning and memory performance, but also observable changes in brain activity. All these works are part of a larger, randomized clinical study, the MEMREHAB trial, in which the efficacy of the mSMT to improve learning and memory was investigated (Chiaravalloti et al., 2013). According to the authors, determining other cognitive domains that benefit from the mSMT could maximize the applicability and utility of this memory retraining technique. Therefore, they also examined the role of processing speed on treatment efficacy with a post-hoc analysis (Chiaravalloti & DeLuca, 2015) and, more intriguingly, the changes in functional brain activity on a working memory task following mSMT treatment (Huiskamp et al., 2016).

According to a recent meta-analysis, there is evidence from single-case or small group studies that memory rehabilitation may be useful for people with MS, but findings from RCTs and systematic reviews have been inconclusive (das Nair, Martin & Lincoln, 2016). In an update of the Cochrane review about memory rehabilitation in MS, the same authors sought to determine whether people with MS who received memory rehabilitation showed better outcomes in their memory functions and functional abilities, in terms of activities of daily living, mood, and quality of life, compared to those given no treatment or receiving a placebo control. RCTs or quasi-randomized trials of memory rehabilitation

or cognitive rehabilitation were selected for a total of 15 studies, involving 989 participants. The interventions included various memory retraining techniques, such as computer programs and training on internal and external memory aids. Results showed that memory rehabilitation was effective in improving memory performance on objective assessments across immediate and long-term follow-ups, but found no difference between intervention and control in subjective memory measures. Some improvements were also demonstrated in quality of life for the intervention group in the immediate follow-up; while no significant effect of treatment was found in either immediate or long-term on mood, immediate functional abilities, and long-term quality of life. The authors concluded that their meta-analysis supports the effectiveness of memory rehabilitation on memory function, as well as on quality of life. However, the evidence was limited and the objective measures used were not ecologically valid, and thus potentially reduced the generalizability of these findings into daily life.

2.2.1.2 Attention and speed of processing

Attention and mental processing speed are two cross-cognitive abilities, whose functioning is capable of influencing the efficiency of all other domains and general cognition. Since many tests labeled as 'attention tasks' may possibly involve processing speed or executive control, it is difficult to find a 'pure' measure of any cognitive domain as well as to draw the conclusions about the impact of MS on these functions (Chiaravalloti & DeLuca, 2008). It is therefore not possible to isolate the effect of attention and processing speed on other cognitive abilities, but their modulatory activity on such processes can be measured.

Attention is defined as the act or state of applying the mind to something. A concentration of the mind on a single object or thought preferentially selected from an input complex, with a view to limiting or clarifying the receptivity by narrowing the range of stimuli. Attention is involved in any activity that is not fully automated and attentive resources are able to optimize the processing of information. Indeed, in the perception or storage of stimuli, the efficiency of the cognitive system depends not only on the characteristics of the stimulus but also on the level of attention involved in the process.

This capacity to maintain concentration can be selective, sustained, or divided (shifting) (Lezak, Howieson & Loring, 2004).

Selective attention is the process of focusing on a particular object in the environment for a certain period of time. Since attention is a limited resource, selective attention involves filtering out irrelevant information around us and focusing on the things that demand our attention (Sternberg, Sternberg & Mio, 2012). A typical task of selective attention is the Stroop Colour Word Test (Barbarotto et al., 1998), which highlights the difficulty of suppressing an automatic response (interference effect). This task measures response inhibition and performance is quantified by time to completion. To perform it properly, the reading process, which is automated in the adult reader, must be inhibited, resulting in costs for the subject in terms of increased response time and greater number of errors. People with MS have been shown to be particularly susceptible to this effect, showing a significant decrease in the correct answers (i.e., naming the ink color of words printed in an incongruent color ignoring their meaning) with respect to healthy subjects (Macniven et al., 2008; Muhlert et al., 2014).

Sustained attention is the ability to direct and focus the cognitive activity on specific stimuli, in order to complete any cognitively planned activity, any sequenced action, or any thought. The capacity to keep the attention over time on repetitive tasks, ensuring the same level of performance, requires a continuous allocation of processing resources and an ever-increasing cognitive effort (Sternberg, Sternberg & Mio, 2012). A very common task is the Symbol Digit Modalities Test (SDMT; Amato et al., 2006; Rao, 1990), which is usually administered to MS patients in the oral version. The task is also a measure of processing speed, as it requires to correctly associate each number with the matched symbol as quickly as possible. A low SDMT score is therefore used as an indicator of impaired mental processing and decision-making in people with MS (Drake et al., 2010; Muhlert et al., 2014, 2015).

Divided attention can be defined as the brain's ability to attend to two different stimuli, acitivities, or ideas at once. Also known as multitasking, individuals do this all the time. The prudent allocation of the available attentional resources allows to process different information sources and successfully respond to the multiple demands of the surrounding. Nevertheless, divided attention decreases the amount of attention being placed on any one task or idea if there are multiple focuses going on at once. In some

cases, cognitive activity is forced to shift attention from one task to another (Sternberg, Sternberg & Mio, 2012). A widely employed task in both clinical and research settings is the Paced Auditory Serial Addition Test (PASAT; Amato et al., 2006; Rao, 1990), which is administered via audiotape and requires each new digit to be quickly added to the one immediately prior to it. PASAT assesses flexibility as well as calculation ability, but is mainly used, like SDMT, as a measure of the auditory information processing speed to discriminate MS patients from healthy controls (Bodling, Denney & Lynch, 2012; Drake et al., 2010; Wojtowicz, Omisade & Fisk, 2013).

Processing speed is a basic cognitive process that sub-serves many other higher-order cognitive domains and refers to the time required to access the necessary information for the undertaken task (Chiaravalloti & DeLuca, 2008). Among these higher domains is executive functioning, a rather extensive construct that involves the organization of behaviors and responses, selective attention to pertinent information and suppression of unnecessary information, and maintenance and shifting of cognitive sets. Processing speed is not dependent on executive functioning, but it is one of the basic cognitive processes driving executive functions. Reduced processing speed is the most widespread cognitive deficit in MS. It has been observed in all disease subtypes and can be used to predict long-term cognitive decline (Bergendal, Fredrikson & Almkvist, 2007; Chiaravalloti & DeLuca, 2008; Genova et al., 2012). This impairment is typically seen in conjuction with other cognitive deficits that are common in MS, including working memory and long-term memory (Genova et al., 2012; Leavitt et al., 2014b; Lengenfelder et al., 2006). Although individuals with MS tend to have difficulty with such tasks, a still-debated issue is whether poor performance is due to executive deficits *per se* or whether it is mainly the result of slowed processing speed.

Rehabilitation

As mentioned earlier, the most recent publications have focused on the rehabilitation of other abilities, including executive functions, attention and processing speed (Amato et al., 2014; Cerasa et al., 2013; Filippi et al., 2012; Mattioli et a., 2010; Parisi et al., 2013; Sastre-Garriga et al., 2011; Vogt et al., 2009). This change in approach seems to have led to more favorable effects on cognitive skills, although findings are still preliminary.

Mattioli and colleagues (2010) demonstrated the effectiveness of an intensive cognitive rehabilitation program, showing better performance in tests of information processing, attention and decision-making, and improved depression scores. More recently, Amato and colleagues (2014) used a computer-based attention processing training program that targeted sustained, selective, alternating, and divided attention. They found a significant improvement on the PASAT, but there were no significant differences between groups on scores of other cognitive skills, including alternating and selective attention. Similarly, a pilot study investigated the effect of computerized cognitive training focused on improving processing speed and working memory (Hancock et al., 2015). The active training group showed an increased performance on a measure of processing speed and attention (PASAT) following cognitive training, but did not demonstrate improvements on tasks generally considered to be purer measures of processing speed (e.g., SDMT, Stroop task) and working memory (Letter-Number Sequencing, Digit Span Backward). The study of Chiaravalloti & DeLuca (2015) represents a post-hoc analysis of a previous RCT to examine the influence of processing speed on the benefits from mSMT treatment. In their cohort, the treatment group showed a significantly improved learning slope in a verbal learning test compared to the post-treatment placebo group. Results also showed that SDMT performance was a significant predictor of benefit from mSMT treatment, beyond group assignment, and was significantly correlated with general cognition, indicating that the SDMT can serve as a proxy for overall cognitive impairment. Given that processing speed is a cross-cognitive function that can influence higher-order cognition, the authors suggested that the best treatment plan for such patients would be to treat the processing deficit first, because, once processing speed is improved, the new learning and memory deficit may no longer exist. Alternatively, the patient could then undergo a memory intervention known to be effective, such as mSMT. Current findings highlight the importance of the treatment selection based on the neuropsychological profile of patients and the development of cognitive rehabilitation modules that effectively address deficits in new learning and memory as well as processing speed.

Even more interesting are the results of the functional magnetic resonance (fMRI) correlates of the attention treatment. One of the first task-based studies was carried out by Sastre-Garriga et al. (2011) to investigate the effect of a cognitive rehabilitation

program on brain activity during the PASAT test. After rehabilitation, patients showed increased brain fMRI response only in the cerebellum when compared with healthy subjects, in addition to an improved performance in backward version of the digit span. Furthermore, Cerasa and coworkers (2013) reported positive effects in MS patients, demonstrating that an intensive computer-based program specifically tailored for impaired attention abilities improved cognition and yielded adaptive neural plasticity of the associated neural network. Stroop test performance improved in the active group only, which also showed increased activation of brain areas sub-serving refreshing phonological stimuli and short-term information storage, i.e. the right posterior cerebellar lobule and left superior parietal lobule. The authors suggested that excessive activity of these two regions could represent a new endophenotype for future cognitive rehabilitative approaches. This hypothesis was also tested by Filippi et al. (2012), showing that a cognitive program focused on attention and information processing was able to enhance neural activity in the parieto-prefrontal regions during the Stroop task. Their results also showed a significant treatment effect in several cognitive-related resting-state networks, including the anterior cingulate cortex (salience processing), left dorsolateral prefrontal cortex (executive function), right inferior parietal lobule, posterior cingulate cortex, and/or precuneus (default-mode network). The authors concluded that rehabilitation of attention, information processing speed, and executive function enhanced the recruitment of brain networks sub-serving the trained functions. Subsequently, the same research team investigated whether the benefits of this cognitive rehabilitation persisted six months after the end of the treatment. Results showed that changes in resting-state functional connectivity of cognitive networks contributed to explain the persistent effects of cognitive rehabilitation at follow-up (Parisi et al., 2013).

2.2.1.3 Information processing efficiency: working memory vs processing speed

The efficiency of cognitive processing depends on the ability to maintain and manipulate information in the brain for a short time period and the speed with which these data are processed (Lezak, Howieson & Loring, 2004). Although impairments have been observed in both working memory and processing speed, the interaction between these two deficits

and the relative contribution of each to the impaired processing ability in MS are controversial (DeLuca et al., 2004; Parmenter, Shucard & Shucard, 2007).

Working memory, also defined as online memory, is a temporary storage and an information manipulation system, which operates for a few seconds and requires a great level of attention. The storage has a period length of about 20 seconds and may contain more or less 7 items, i.e. information chunks, such as couples or triads (Baddeley, 1992). Working memory is regulated by the dorsolateral prefrontal cortex and is involved in complex cognitive tasks such as reasoning, comprehension and learning (DeLuca et al., 2015): it can be imagined as a blackboard to do mental calculations or to write down words for a few seconds while trying to complete a task. This is a very important function of which individuals are often unaware.

According to Baddeley's model (1992), working memory consists of a central executive system that coordinates, controls and manipulates information processing, and two "slave systems", the phonological loop and visuospatial sketchpad, which maintain and temporarily store verbal and visual information. Impairments in both the central executive and slave systems within the working memory have been documented in MS population (D'Esposito et al., 1996; Grigsby et al., 1994a, 1994b; Rao et al., 1993; Ruchkin et al., 1994). For instance, several investigations have reported deficits in the central executive system, especially in allocating attentive resources and manipulating information. When compared with healthy participants, MS individuals with different disease courses demonstrated difficulty in tasks that required the manipulation of stored information, including Digit Span Backward, SDMT and PASAT (Drake et al., 2010; Grigsby et al., 1994a, 1994b; Wojtowicz, Omisade & Fisk, 2013).

Although working memory disorders have been well-established in MS, it remains to be clarified whether these impairments are due to working memory damage alone or if they are confused with processing speed deficit (DeLuca et al., 2004; Parmenter, Shucard & Shucard, 2007). According to Genova et al. (2012), many of the previous studies have employed a methodology incorporating a "speed versus accuracy confound", which states that as an individual is required to process information more quickly, performance accuracy generally decreases (D'Esposito et al., 1996; Grigsby et al., 1994a, 1994b; Rao et al., 1993). This hypothesis has been extensively studied in aging. For example, Salthouse (1996) showed that most of the variance in age-related episodic memory loss

can be attributed to processing speed deficits. However, this confusion in speed measurement versus accuracy makes it extremely difficult to attribute whether individuals with MS have problems in working memory, speed, or both.

There is some support for the hypothesis that MS people, when given adequate time, perform at the same level of accuracy as healthy adults. Recent studies on this subject suggest that processing speed contributes more to inadequate processing of information than working memory deficits (DeLuca et al., 2004; Kalmar et al., 2008; Lengenfelder et al. al., 2006; Parmenter, Shucard & Shucard, 2007). These authors have demonstrated that subjects with MS are able to achieve accuracy comparable to healthy individuals, but need significantly longer time to process information. Their results suggest that when working memory load is low, increasing the amount of time it takes to process the task can significantly improve performance, even at 'normal' levels. Taken together, these studies support the hypothesis that contrary to what has been previously proposed (D'Esposito et al., 1996; Grigsby et al., 1994a, 1994b; Rao et al., 1993), the main information processing deficit in people with MS may be the slow processing speed and not the working memory accuracy. In other words, MS subjects may take longer to process information before they can use their working memory systems. Many of these authors have also pointed out that this decreased efficiency would affect the ability of MS individuals to learn new information and perform higher-level cognitive functions (DeLuca, Barbieri-Berger & Johnson, 1994; DeLuca et al., 1998, 2004; Lengenfelder et al., 2006). There are at least two possible explanations proposed by DeLuca and colleagues (2004) for differential effects on the processing speed and working memory among MS people, namely the Relative Consequence Model and the Independent Consequence Model.

The first model suggests that individuals with MS have a core problem in processing speed, which in turn results in difficulties in other cognitive processes (DeLuca et al., 2004). More precisely, the Relative Consequence Model hypothesizes that difficulties in working memory, and likely other cognitive functions, are primarily a function of impaired processing speed. As the magnitude of processing speed deficit increases, a critical point is reached leading to an impact on working memory performance. Therefore, this model predicts that inefficiencies in other cognitive processes are a by-product of slower cognitive processing. As noted above, the

aforementioned hypothesis has received considerable support in the aging literature (Salthouse, 1996).

The second potential explanation, termed the Independent Consequence Model, is that deficits in processing speed could be independent, but not mutually exclusive, from working memory impairments. The specific pattern of cognitive deficits would then be determined by individual factors, including brain lesion or depression. However, this would assume a relative homogeneity in lesion location, pattern, severity, and so forth, which is unlikely in MS. Given the high heterogeneity of the disease, these factors may contribute to additional cognitive deficits (e.g., working memory) in some MS individuals that are not present in others. At one level, this hypothesis could be consistent with RRMS subjects that usually display a primary deficit in processing speed. As the disease progresses and develops into SP phase, specific areas of brain involvement, such as axonal degeneration and NAWM abnormalities, can increase leading to additional problems in other cognitive functions, including working memory (DeLuca et al., 2004). In this case, people with MS may have both deficits that are independent of each other, perhaps due to individual disease factors. As a result, no matter how much time these participants are provided to improve their performance, they are simply unable to carry out complex working tasks. Unlike the first hypothesis, the Independent Consequence Model predicts that processing speed and other cognitive processes are more a function of specific areas of brain involvement, rather than of overall cerebral integrity. Clearly, a combination of both models can better account for the observed pattern of deficits in MS.

This situation confounds the assessment of cognition in MS, which could lead to a misinterpretation of testing results. Information processing speed is typically evaluated on the basis of performance accuracy on speeded clinical neuropsychological tests; and a reduced number of correct responses is inferred to reflect slowed information processing (Bodling, Denney & Lynch, 2012; Drake et al., 2010; Muhlert et al., 2014, 2015). By definition, the commonly used tests in MS have a speed component and range from simple reaction time to complex, demanding cognitive operations. Seven task categories based on their methodological approach can be identified (i.e., symbol/digit substitution, working memory, executive functions, reaction time, attention, self-report questionnaires, and other) (Costa et al., 2017). Traditionally thought of as a working memory test with speed demands, PASAT was widely employed in the 1990s and early 2000s. Score

impairments in this task are more associated with processing speed rather than working memory deficits (Forn et al., 2008). As the speed at which the PASAT item is presented increases, it is common that people with MS give 'late responses' for which they are classified as impaired. This means that participants are able to properly manipulate the numbers within their working memory, but are unable to do it quickly at a faster level. In other words, not counting late responses penalizes subjects for being slow. Conversely, considering late responses as correct is likely to accommodate potential processing speed deficits, making PASAT more a test of working memory accuracy (Balzano et al., 2006). In addition, it has recently been argued that accurate PASAT performance requires multiple cognitive domains and is also influenced by emotional burden, thus it may not be an ideal measure of processing speed. In contrast, accumulating evidence over the last decade has demonstrated the SDMT to be sensitive to processing speed deficits in MS with a relatively low working memory load. For all these reasons, SDMT has been proposed as an alternative to PASAT, as it shows a slightly better ability to predict disease course, diagnosis and disability, and a good correlation with MRI findings (Drake et al., 2010; Parmenter, Shucard & Shucard, 2007).

The definition of the information processing speed as well as its theoretical conceptualization are still debated. Studies in this field can be organized according to one of the three main definitions of processing speed: (1) the amount of time needed to perform a cognitive task or the amount of work done within a certain period of time; (2) a complex construct resulting from the interaction of multiple factors; and (3) in physiological terms, the speed with which the brain can process information. While the first two categories were applied in articles published in the past decade, the relevance of the physiological aspect of processing speed has gained more attention in recent years, starting from 2013, and is strongly associated with the evolution of neuroimaging methodology (Costa et al., 2017). Several theoretical models have been proposed to facilitate our understanding of the processing speed deficits in MS. The most commonly used was the aforementioned model of the relative consequence proposed by DeLuca et al. (2004), followed by the theory of the limited time mechanism of Salthouse (1996). The latter postulates that processing speed deficits are related to significant delays within the early steps of information processing and that previous cognitive products may be lost when the next processing is completed. These theoretical models were not used as

attempts to explain and understand processing speed deficits *per se*, but rather to describe the interaction between cognitive functions and/or systems, for example between processing speed and working memory (DeLuca et al., 2004; Salthouse, 1996). They do not deepen our understanding of the etiology of processing speed deficit itself.

Very recently, Costa and colleagues (2017) have proposed the 'tri-factor model of processing speed' impairments in MS based on the premise that this is not a unitary construct. Information processing is known to be composed of several steps, starting with the input of information into the sensory system, continuing with the cognitive task performance and extending to the motor output (action or behavior). Each of these processes must take place very quickly in order to successfully accomplish the task with time demands, i.e. processing speed, and can be individually affected by brain pathology. This new tri-factor model has several implications for the assessment and rehabilitation of processing speed. A complex task such as SDMT requires processing at all three levels and is thus sensitive to detect any impairment, but it does not allow the separation of the particular aspect of processing speed that is deficient in people with MS. Therefore, it would be desirable to systematically evaluate all three levels to truly understand the clinically meaningful changes and the nature of processing speed deficits in MS: sensorial speed (e.g., contrast sensitivity tests, optic coherence tomography, and event-related potentials), cognitive speed (cognitive tests), or motor speed (e.g., speech tests and eye tracking). According to the authors, a better understanding of these aspects would guide the development of rehabilitation programs, which could then be designed to target the specific speed deficit.

Rehabilitation

Clarifying the source of processing impairments in MS is essential to improve our ability to take care of these individuals as well as to improve their cognition and everyday life functioning. Several researches have been conducted to verify the effectiveness of cognitive rehabilitation techniques in people with MS, although such treatment protocols do not specifically address processing speed independently of other disease-related impairments (Mattioli et al., 2010; Vogt et al., 2009).

In the study by Vogt et al. (2009), two different cognitive rehabilitation schedules, high intensity versus distributed rehabilitation, were compared. The program was a

specific working memory treatment consisting of three modules: City Map to train spatial orientation, Find Pairs to train the updating function of working memory, and Memorize Numbers to train short-term memory while performing an arithmetic distraction task. Results showed that cognitive rehabilitation significantly improved working memory and mental speed performance. Since no difference was found between the high intensity and distributed groups, the authors concluded that cognitive rehabilitation *per se* led to independent improvements.

Until effective treatments for processing deficits in MS are identified, an immediate means of improving cognition in this population may be to provide individuals more time to process information, in order to maximize cognitive functioning in other areas, like learning new information. It has been demonstrated that the presentation speed of verbal stimuli significantly influences the ability to retrieve information in MS people. In a study by Arnett (2004), a slower presentation allowed subjects to recall a greater amount of information on a story learning task. From this work, it can be concluded that slowing the presentation of to-be-learned information could significantly improve learning and memory in rehabilitation settings. Alternatively, research in other populations, such as healthy elderly adults, has shown that processing speed deficit can be effectively treated with a behavioral intervention and these benefits may also be generalized to day-to-day living in that population (Edwards et al., 2005). It is important to note that cognitive dysfunctions in MS are similar to those observed in aging, as processing speed impairments have a significant impact on higher-level cognitive functioning (Salthouse, 1996; Salthouse & Ferrer-Caja, 2003). One could therefore hypothesize that techniques that have shown to improve this ability in aging would be likely to have similar effects in people with MS.

The recent findings on neuropsychological rehabilitation, enhancing the functioning of neural networks, are promising, suggesting that increased connectivity of specific brain areas after training might reflect the occurrence of compensatory mechanisms, which can be promoted through training. Bonavita and colleagues (2015) performed a non-randomized parallel-group trial to better understand the effects of short-term computer-based cognitive rehabilitation on cognitive performance and default-mode network intrinsic functional connectivity in cognitively impaired RRMS patients. Both the active and control groups underwent an extensive neuropsychological evaluation and

resting-state fMRI study at the entry and at the end of follow-up. Several cognitive tests of information processing speed and verbal and visual sustained memory improved in the active, but not in the control, group after the 8-week study period. Likewise, increased resting-state functional connectivity in the posterior cingulate cortex and inferior parietal cortex bilaterally, sub-serving the default-mode network, was found in the active group. This exploratory work suggests that computer-based cognitive rehabilitation may induce an adaptive cortical reorganization that promotes better cognitive performance, thus reinforcing the value of cognitive exercise in the general perspective of building cognitive or brain reserve. In a similar study exploring the effectiveness of home-based, computerized, cognitive rehabilitation with the same software, Campbell et al. (2016) found that the treatment group showed a greater improvement in SDMT gain scores between the baseline and 6-week follow-up compared to the control group, and exhibited increased activation in the bilateral prefrontal cortex and right temporoparietal regions relative to control group after a further 12 weeks. Pedullà and coworkers (2016) investigated the effects of an adaptive versus a non-adaptive cognitive training on cognitively impaired people with MS. This program was administered by means of a customized application software delivering personalized working memory-based exercises. The study group underwent an adaptive training characterized by the automatic adjustment of task difficulty to the subjects' performance, while the control group was trained at constant difficulty levels. A significant improvement was found only in the intervention group in tests evaluating verbal memory acquisition and delayed recall, verbal fluency, sustained attention, concentration and information processing speed. This effect was maintained also after 6 months. The authors concluded that a personalized training and an adaptive working load are crucial features that determine the effectiveness of rehabilitative treatment, allowing transfer effects to several cognitive domains and long-term maintenance of results. As mentioned earlier, the research group of Huiskamp et al. (2016) conducted a secondary analysis of data from a larger double-blind, placebo-controlled RCT to examine changes in cerebral activation on a working memory task following mSMT treatment. Significant increases in cerebral activation were noted in the dorsolateral prefrontal cortex, supplementary motor area and inferior parietal lobule at follow-up in the treatment group, while no significant changes were found in the placebo control group. According to the authors, the observed pattern of activation of the

frontoparietal network suggests that the mSMT treatment protocol may be moving toward the restoration of neural activation patterns during working memory task. Although mSMT training seems to be more effective in improving new learning and memory, the effects on cerebral activation patterns are also generalized, increasing the recruitment of attention- and working memory-related neural networks.

2.2.1.4 Executive functioning skills

The term executive functioning refers to a set of cognitive abilities necessary for complex goal-directed behaviors and adaptation to environmental changes or needs (Chiaravalloti & DeLuca, 2008). This is rather generic and ambiguous, as it suggests a type of unitary system, whereas it is composed of complex interrelated subsystems. Although cognitive abilities have not been well-defined, they include problem-solving, planning, initiation and inhibition of responses, strategic thinking, abstract and conceptual reasoning, working memory, verbal fluency, cognitive flexibility or set-shifting, and changes in behavior (Goldberg, 2001). This vague definition of executive functions is partly responsible for the confusion and heterogeneity observed in the studies of different neurological diseases including MS.

The investigation of executive functions in MS is relatively recent. The first works were published in the 1980s and consistently established the impairment of executive functioning in the disease and its neuropathological correlates (Foong et al., 1997; Peyser et al., 1980). Even though studies are not comparable due to the high methodological variability, it is generally accepted that several abilities are compromised at different levels of severity and frequency (20-80%) (Cerezo García, Martín Plasencia & Aladro Benito, 2009; Drew et al., 2008; Foong, et al., 1997). Predominant impairments are seen in categorization, abstract reasoning, verbal fluency, working memory, planning, and mental flexibility, though less frequently than deficits in memory and processing speed (Rao et al., 1991a; Bobholz & Rao, 2003).

Drew and coworkers (2008) carried out a systematic evaluation of executive functions in a large community-based sample of MS diagnosed individuals and noted that 17% of patients showed difficulties across a range of executive abilities, including inhibition, shifting and verbal fluency. Tests of verbal fluency evaluate the spontaneous

production of words under restricted search conditions, such as words that begin with a specific letter (phonemic) or words from a particular category (semantic) (Novelli et al., 1986). Although MS patients report significant deficits in both, the phonemic fluency measures are among the most validated indicators of executive dysfunction, because they impose substantial demands on information processing speed and language skills (Crawford & Henry, 2005; Henry & Crawford, 2004). In the context of MS specifically, measures of verbal fluency are among the most sensitive markers of cognitive dysfunction (Henry & Beatty, 2006).

A frequent methodological problem for clinicians who evaluate executive functions is the use of time-dependent tasks. Since many executive tests are performed within a certain time window, caution is needed before interpreting disorders in high-order cognition when there is a processing speed component (Chiaravalloti & DeLuca, 2008). For this reason, in evaluating executive functioning, it is desirable to use both speed based and non-speed based tasks whenever possible. For people with MS, the combination of processing speed and executive functions holds important implications for their daily living. For instance, the feeling of being overwhelmed by workplace responsibilities often described by patients can be addressed by the understanding that their problems are limited to the slow processing speed and that they can improve it with appropriate accommodations, such as allowing themselves extra time for the activities (Leavitt et al., 2014b).

The Wisconsin Card Sorting Test (WCST; Laiacona et al., 2000) is a typical non-time-based task, measuring the ability to create abstract concepts, to change and maintain the set, and to use feedback. Already in the early studies using WCST, significant impairments in the ability of concept formation and problem-solving were frequently observed in MS individuals. It was seen that especially chronic-progressive patients were less able to formulate and eliminate irrelevant hypotheses, respond to environmental feedbacks to switch to other strategies or sets, and thus tended to produce more perseverative errors (Arnett et al., 1994; Parmenter, Shucard, & Shucard, 2007; Rao, Hammeke & Speech, 1987). In particular, Parmenter et al. (2007) found that WCST was also modestly related to MRI indexes of brain atrophy and lesion burden as well as to the vocational status of patients. Although widely accepted as an executive function test, there is no consensus among the studies reporting mixed results on WCST deficits

(Leavitt et al., 2014b). Recent research has shown that worse WCST scores were more prominent in progressive MS patients, but were less capable to discriminate between recurrent forms and healthy controls (Cerezo García, Martín Plasencia & Aladro Benito, 2015; Leavitt et al., 2014b). More precisely, Leavitt and colleagues (2014b) have found that there were no group differences between MS and healthy individuals and no relationship between brain atrophy and performance on an executive task that required no processing speed demands (i.e., WCST). Their findings suggest that people with MS do not have executive deficits independent of the slow processing speed. Therefore, the authors have pointed to two likely explanations. On the one hand, it is possible that executive deficits experienced by people with MS in everyday life, such as difficulty in multitasking, cannot be captured or sufficiently quantified by cognitive measures, since real-life demands are difficult to replicate in a controlled laboratory setting in which testing takes place. On the other hand, the authors have suggested that independent executive deficits emerge later in the course of the disease, and inter-individual heterogeneity of the lesion load can lead to executive deficits in some but not all subjects. Their hypothesis was suggested by the observation of a very small subgroup with the most severe atrophy that revealed a significant association between brain volume reduction and non-speeded executive measures (perseverative errors and perseverative responses) of the WCST. This result was also consistent with DeLuca et al. (2004) showing that the RR and SP courses had prominent processing speed deficits, but working memory impairment was only evident as an independent deficit in the SPMS.

Rehabilitation

Because of their superordinate, supervisory role, executive function processes are involved in many aspects of everyday life, especially those that are not routine or automated. Executive functions could, in principle, be improved through direct training and, due to their involvement in all new and challenging tasks, could also be ameliorated with cognitive training of other skills (Amato et al., 2013a).

There are a few re-training programs that have specifically targeted executive functions (Amato et al., 2013a). In the double-blind, placebo-controlled study by Fink et al. (2010), MS patients showed that executive functions and verbal learning were significantly improved and this treatment effect was stable over one year, illustrating that

their findings were lasting and not just transitory. Another interesting work was by Tesar and colleagues (2005), in which overall the MS treated group showed improvement on executive functioning compared to the MS control group receiving non-specific rehabilitation, and the benefits were stable at 3-month follow-up. It is worth noting that the overall compensatory strategy package received by all treatment groups included building up routines of behavior, problem-solving and planning, which could explain the improvement in executive test scores. However, Solari et al. (2004) reported that an isolated computer-assisted memory and attention rehabilitation was no better than a non-specific intervention in improving these functions. All the above evidence suggests that no definite conclusions can be drawn about the effects of these factors on rehabilitation outcomes.

An intriguing study by Mattioli and colleagues (2016) tested whether combining attention training with anodal transcranial direct current stimulation (a-tDCS) over the left dorsolateral prefrontal cortex could improve training efficacy. Patients showed a significantly greater improvement in SDMT and WCST after treatment and in PASAT-2 and WCST six months later. They also had significantly shorter time to reach the most difficult exercise level, compared to sham treatment. These results indicate that a-tDCS on the dorsolateral prefrontal cortex during cognitive training promotes improvements in attention and executive functions in MS patients and shortens treatment duration.

A stimulating growing field of research that is worth mentioning is virtual reality as a relatively new intervention tool in rehabilitation, allowing to simultaneously engage the subject in cognitive and motor activities. With the advent of modern technological advances in healthcare, approaches towards rehabilitation, treatment, and cognitive remediation are moving to an online platform that can be adaptive and personalized. One of the main advantages of this approach is the study of cognitive training programs in a real-world setting, providing the participants with access to the intervention from home with remote supervision. This allows for rapid study enrollment, strong program compliance, and relatively low cost when considering for real-world use. A recent pilot RCT attempted to determine the feasibility of an 8-week, hybrid-variable training program using a video-game platform, with the aim of achieving broad transfer effects across multiple cognitive domains (Janssen et al., 2015). Results indicated an overall improvement in game-related skill acquisition and evidence for the feasibility of the

intervention, but a lack of transfer to cognitive functioning tasks. Despite this limitation, the training group showed improvements on a measure of short-term visuospatial memory. De Giglio and colleagues (2015) performed a randomized, wait-list controlled study to investigate the effectiveness of an 8-week home-based cognitive rehabilitation program based on the video-game of Dr. Kawashima's Brain Training (DKBT; Nintendo, Japan), including tasks of memory, attention, processing speed, working memory, visuospatial processing, and calculations. The active group exhibited a significant improvement in sustained/divided attention (PASAT), some aspects of executive functions (Stroop test) and quality of life, and cognitive fatigue. In a post-hoc analysis, 24 patients enrolled in the original trial underwent resting-state fMRI before and after the game-based cognitive training (De Giglio et al., 2016a). The authors found an increased thalamic functional connectivity in brain areas corresponding to the posterior component of the default-mode network (cingulum, precuneus, and bilateral parietal cortex) and a decreased connectivity in the cerebellum (vermis) and left dorsolateral prefrontal cortex. Positive correlations were also observed between improved cognitive performance (PASAT, SDMT, and Stroop test) and increased functional connectivity in areas belonging to the default-mode network. These findings show the relevance of thalamic regulation of the brain networks involved in cognition. They suggest that changes in thalamic resting-state network connectivity may represent a functional substrate for cognitive enhancement associated with a video game-based rehabilitation program. The same researchers subsequently acquired brain images from a subgroup of 18 of the original 24 patients to investigate whether their rehabilitation program also induced structural changes in WM tracts that are crucial to cognitive functions, focusing on the microarchitecture of corpus callosum (De Giglio et al., 2006b). They concluded that a video game-based cognitive rehabilitation may induce significant microstructural changes in the corpus callosum; and that these adjustments are associated with an improvement in cognitive performance (PASAT). The study by Charvet et al. (2017) is the largest clinical trial of cognitive rehabilitation in an MS sample, with a total of 135 participants. This research group examined whether an adaptive online cognitive training program at home was superior to an active control of playing ordinary computer games for improving cognitive functioning in adults with MS. The benefit was measured by changes in a composite score of neuropsychological tests and was overall modest. No one

measure indicated a specific response to the training, but the majority of cognitive measures changed in a direction that favored the adaptive program. According to the authors, the lack of specificity could be attributed to the widespread effects of a better cognitive processing speed across a range of measures, mediated by individual differences in baseline performance. This tele-rehabilitation approach provides evidence that adaptive, computer-based cognitive remediation accessed from home can improve cognitive functioning in MS.

Studies on cognitive rehabilitation are somewhat more consistent than those on motor rehabilitation, not only in terms of trained functions but also in their results (Prosperini et al., 2015). Despite some differences regarding the neuropsychological scales and clinical outcome measures adopted, task-related fMRI and resting-state fMRI findings are quite consistent, pointing out the involvement of some specific brain regions such as the cingulate cortex (Bonavita et al., 2015; Chiaravalloti et al., 2012; De Giglio et al., 2015; Filippi et al., 2012; Sastre-Garriga et al., 2011), precuneus (Chiaravalloti et al., 2012; De Giglio et al., 2015; Filippi et al., 2012), and cerebellum (Cerasa et al., 2013; Chiaravalloti et al., 2012; Leavitt et al., 2014a; Sastre-Garriga et al., 2011). The cingulate cortex is known to deal with the formation and processing of emotions, learning and memory, thus linking behavioral outcomes to motivational feelings (Hayden & Platt, 2010). The precuneus is involved in episodic memory and visuospatial imagery and it has been suggested as a specific target for visual mirror therapy and virtual reality-based rehabilitation (Dohle et al., 2011). Being connected with many association networks, the involvement of the cerebellum has been now recognized not only in motor planning and learning, but also in different high-order cognitive domains, including attention, memory and learning, executive control, language, and visuospatial functions (Buckner, 2013; Koziol et al., 2014).

2.2.1.5 Visuospatial and visuoconstructive abilities

Visual disturbances are among the most common symptoms reported by about a quarter of MS people. Abnormalities in primary visual processing, mainly due to optic neuritis, may have a detrimental effect on visual perceptive processing and contribute to difficulties in higher-order cognitive tasks that have visual demands. Although WM

lesions of parietal-temporal-occipital areas are frequent in MS, deficits of visuospatial and visuoconstructive abilities observed in approximately 25% of patients have rarely been investigated with respect to studies on long-term memory and information processing efficiency (Bruce, Bruce & Arnett, 2007; Rao et al., 1991a ; Vleugels et al., 2000).

While visuospatial dysfunction translates into a deficit in image representation and integration, in spatial localization and object tracking, visuoconstructive impairments lead to difficulties in spatial organization of visual information, assembly and drawing. Both these functions require the integrity of visual processing pathways, including the occipitoparietal or dorsal (magnocellular) paths responsible for movement analysis and visuomotor coordination, the inferior occipitotemporal or ventral (parvocellular) paths related to the perception of shape and color of objects, and the medial superior temporal area necessary for visuospatial functions (Marasescu, Cerezo García & Aladro Benito, 2016). Although not many researches concerning this topic have been conducted so far, a newly published paper has stated that there is a correlation between visual processing deficits and a higher limitation in visual temporal processing capacity. In other words, their findings have revealed a strong relationship between latent sensorial temporal limitation of the visual system and processing speed deficits in MS (Lopes Costa et al., 2016). With regard to spatial and constructive visual functions, another recent study has investigated the relationship between these abilities and lesion volume on the parietal-temporal-occipital association area and subcortical atrophy (bicaudate ratio and third ventricle width) in MS patients (Marasescu, Cerezo García & Aladro Benito, 2016). In their work, the authors have used tests that are not routinely employed for cognitive assessment in MS, but are specific and widely validated for evaluating these functions in a number of countries. In particular, the Rey-Osterrieth Complex Figure (ROCF; Caffarra et al., 2002) is a well-known tool that analyses complex visual perception and organization, and strategy planning to resolve problems, in addition to visuomotor and visuoconstructive abilities. Their results have shown that all measures of regional lesional volume and brain atrophy are significantly and inversely correlated with visual abilities, and the third ventricle width is the strongest predictor of visuoconstructive performance, including ROCF. While the increased bicaudate ratio is related to extensive frontal atrophy of WM, the raised third ventricle width is associated with the volume of the

thalamus, which has extensive cortical connections with frontal brain areas. This connectivity is hypothetically necessary to perform complex activities involving the organization and praxis functions, and the thalamus appears to be one of the brain regions with a higher prevalence of atrophy during the initial stages of MS (Marasescu, Cerezo García & Aladro Benito, 2016).

Rehabilitation

As for visuospatial deficits, these are less frequent and are re-trained within more comprehensive rehabilitation protocols such as those already mentioned. For instance, Brenk and colleagues (2008) utilized a short-term non-specific home-based 6-week cognitive training and found improvements in visuoconstructive and long-term visual memory when compared to non-MS controls. Furthermore, prior depressed mood and quality of life improved in MS patients during the training period and remained steady up to 6 months. This study suggests that mental training, although unspecific, leads to improvements in several cognitive and personal skills.

There is a growing interest in a new program referred to as 'MS-line! Project' recently proposed by a group of researchers (Gich et al., 2015b). MS-line! was developed from neuroimaging studies showing brain neuroplasticity or compensatory mechanisms in the early stages of MS before the appearance of cognitive decline. This is a new, freely available, cognitive rehabilitation program for MS patients that can be used at home from the initial stages of the disease without affecting daily activities, and is aimed at functional restitution based on the hypothesis of neuroplasticity. The program offers a wide range of exercises: mathematical, problem-solving and word-based tasks; physical materials that include spatial, coordination and reasoning games; computer-based materials which involve logic and reasoning, working memory and processing speed games. Written, manipulative, and computer-based materials with up to five difficulty levels with clues and an attractive design to enhance adherence have also been included. This program stems from the identification of a gap between the initial diagnosis and the moment when patients begin neurorehabilitation. Although validation is still required, a pilot study suggests that this program has the potential to achieve this goal by including all those patients with early MS, in which compensatory mechanisms are more evident (Gich et al., 2015a).

2.2.2 Social cognition and theory of mind

Social cognition can be defined as a complex of processes and abilities necessary to regulate interpersonal relationships and enable individuals to act appropriately and flexibly in their social environment (Adolphs, 2001; Frith & Frith, 2005). The core ability of social cognition is represented by the so-called theory of mind (ToM), also defined as 'mentalizing' or 'mind reading', which is based on both cognitive and affective processes (Shamay-Tsoory & Aharon-Peretz, 2007; Stone, Baron-Cohen & Knight, 1998).

Cognitive ToM refers, firstly, to the capacity to appreciate the distinction between the self and others in terms of thoughts, intentions and beliefs, and secondly to understand the mental representations of others. Besides helping to make sense of, and predict, others' behavior, this ability also allows to distinguish real mental states from lies, gaffes, metaphors or sarcasm. This component is usually investigated with verbal 'perspective taking' tasks, like tests of false-belief or indirect speech understanding. *Affective* ToM can be defined as the capacity to have insight into emotional states and feelings of others, and is mostly assessed with visual 'decoding' tasks, like recognition of emotions from gaze or facial expressions (Bora et al., 2016; Shamay-Tsoory & Aharon-Peretz, 2007). ToM recruits a complex neural network that includes the anterior cingulate cortex, orbito-frontal cortex, superior temporal sulcus, temporal pole, amygdala, and temporo-parietal junction (Abu-Akel, 2003; Apperly et al., 2004; Frith & Frith, 2006; Gallagher & Frith, 2003). Interestingly, available data suggest different frontal circuits at the base of ToM sub-components: ventrolateral and dorsolateral prefrontal cortices for cognitive mentalizing; ventromedial prefrontal and orbito-frontal cortices for emotional processing (Shamay-Tsoory & Aharon-Peretz, 2007; Kalbe et al., 2010). Despite the above-mentioned separation, the complex nature of these functions could lead to the overlap of some brain regions and processes (Chalah & Ayache, 2017; Labbé, Ciampi & Carcamo Rodrìguez, 2018).

Disturbances in social cognition (poor ToM, reduced emotion recognition, impaired perception of social rules or abnormal social behavior) are salient features of many neurodevelopmental, neuropsychiatric and neurodegenerative disorders, and acute neurological damage, such as traumatic brain injury, which often affect the frontal lobes and their connections (Baron-Cohen et al., 1999; Blair & Cipolotti, 2000; Brüne, 2005;

Poletti, Enrici & Adenzato, 2012; Ruffman et al., 2008; Saltzman et al., 2000; Shur, Shamay-Tsoory & Levkovitz, 2008). As a prototype of demyelinating diseases, MS-related WM pathology disrupts various neural networks, including frontal intrahemispheric and frontal-subcortical tracts known to be involved in processing of mental states and emotional stimuli, and it is therefore thought to have an impact on social cognition (Poletti, Enrici & Adenzato, 2012; Ruffman et al., 2008). Given the large network implicated in social cognition, available data support the presence of ToM deficits even at early stages of MS, but with a considerable heterogeneity within the MS population in relation to the nature, severity and specificity of ToM impairments (Chalah & Ayache, 2017).

Most of prior studies have mainly focused on the affective component of ToM, using photographs depicting eyes and faces to infer others' mental states. Data from two recent meta-analyses suggest that MS patients have greater difficulty than healthy controls do in using visual cues to determine what another person is feeling (Bora et al., 2016; Cotter et al., 2016). In particular, numerous authors have reported a selective impairment in MS for negative emotions, including sadness, fear and anger (Henry et al., 2009, 2011; Krause et al., 2009; Lenne et al., 2014; Prochnow et al., 2011). Since MS is characterized by a widespread rather than focal brain damage, the relative specificity of failures in recognizing unpleasant emotions is a meaningful element. Interestingly, this pattern of isolated involvement of negative emotions is consistent with studies of other neuropsychiatric disorders, including acquired sociopathy and traumatic brain injury (Blair & Cipolotti, 2000; Prior, Sartori & Marchi, 2003). It should also be noted that five studies have found intact abilities in recognizing emotional facial expression in MS patients (Di Bitonto et al., 2011; Jehna et al., 2010, 2011; Passamonti et al., 2009; Pinto et al., 2012). As for cognitive ToM in MS, evidence is more scattered. This is probably due to the distinction between specific task-types. Using only verbal/non-verbal ToM tests, such as reading a series of written stories, some authors found faulty recognition of false-beliefs or inference of others' intentions in their cohorts of MS (Henry et al., 2011; Roca et al. 2014). Similar results were also achieved by studies using dynamic videotape tasks that presented social interactions (Genova et al., 2016; Kraemer et al., 2013; Pöttgen et al., 2013). In contrast, authors who combined different tools (verbal and non-verbal or video) to evaluate both aspects of ToM (affective and cognitive) obtained heterogeneous

results (Banati et al., 2010; Dulau et al., 2017; Mike et al., 2013; Neuhaus et al., 2018; Ouellet et al., 2010). According to Bora et al. (2016) and Cotter et al. (2016), their reports highlighted specific deficits, for MS patients, in inferring mental states on visual tasks, while verbal tests like the Faux Pas (Stone, Baron-Cohen & Knight, 1998) were performed normally. Such deficits were generally found in patients with relatively short disease duration (eight years on average), mild to moderate degrees of physical disability (2.3 median EDSS score) and relapsing course of illness.

ToM studies have also analyzed several confounding factors such as MS fatigue, high mood scores, cognitive deficits, disease duration, and physical disability as measured by EDSS. Some authors were in favor of an association between ToM deficits and non-social cognitive performance (Cecchetto et al., 2014; Dulau et al., 2017; Henry et al., 2009; Kraemer et al., 2013; Ouellet et al., 2010; Roca et al., 2014) and clinical features, such as EDSS scores (Pöttgen et al., 2013) and progression rate (Banati et al., 2010). Others denied any significant association between ToM performance and demographic or clinical characteristics (Henry et al., 2011), cognitive impairment (Batista et al., 2017; Henry et al., 2011; Phillips et al., 2011; Pöttgen et al., 2013), depressed mood (Kraemer, et al., 2013; Pöttgen et al., 2013; Roca et al., 2014), or fatigue (Roca et al., 2014).

Of all studies mentioned above, only three investigated both cognitive and affective ToM components in very mild RRMS (Henry et al., 2011; Kraemer et al., 2013; Roca et al., 2014). Henry and colleagues (2011) assessed 64 patients with an EDSS ≤ 5.5 using a short version of the Faux Pas test and tasks of recognition of false-beliefs and facial emotions, and showed that patients failed to attribute to others' thoughts and intentionality, as well as to recognize negative emotions. The authors also evaluated the global mental functioning of MS patients, who were mostly cognitively intact, but showed a poorer performance compared to healthy subjects on executive tasks. However, the correlation analysis between ToM impairment and executive functions did not show a significant relationship. Kraemer et al. (2013) used a naturalistic video to measure participants' ability to interpret cognitive states and emotions underlying an explicit message conveyed by a character. Their sample included 25 patients with an EDSS score lower than 2.5 and a maximum disease duration of 24 months from the diagnosis. Patients were able to accurately describe the story of the video, but their reasoning about

characters' thoughts, intentions and emotions was insufficient. The study also evaluated executive functions using tests of capacity of inhibition, working memory and set shifting. Their results showed no significant differences between patients and controls in these tasks, but the performance on the ToM test was significantly correlated with sensitivity to interference as measured by the Stroop task. Finally, Roca and coworkers (2014) administered the Faux Pas test to 18 patients with a maximum EDSS score of 3, and showed that they were impaired at inferring intentions of others, while their ability to identify the emotional states was intact. Using several cognitive tests, the authors found that patients were impaired, compared to controls, on measures of attention, processing speed and cognitive flexibility. When these aspects were correlated with ToM, they found that two executive tasks had a significant association with the ability to detect the *faux pas*, and none with the ability to infer intentionality.

Another important aspect of social cognition deficits in MS concerns the behavioral impact that affects the moral evaluation of the actions of others. So far, only two studies have explored moral cognition in the MS population (Gleichgerrcht, Tomashitis & Sinay, 2015; Patil et al., 2017). Starting from previous reports on the key role of the temporal-parietal junction during moral judgment (Young & Tsoi, 2013) and on the close relationship of reduced empathy and increased alexithymia with moral judgments (Gleichgerrcht & Young, 2013), these two pioneering works explored the ability of individuals to make judgments about moral dilemmas, asking them the permissibility of sacrificing the welfare of the few in favor of the greater good. Both findings confirmed that people with MS had an atypical model of moral judgment, characterized by decreased moral permissibility, increased emotional reactivity to moral transgressions and, in particular, a bias towards believing that the rest of the population would deliver similar moral judgments (Gleichgerrcht, Tomashitis & Sinay, 2015; Patil et al., 2017). Either way, moral cognition among patients with MS remains largely unexplored to date.

In the neuroimaging literature, only a few MRI studies have investigated the neural substrates of social cognition in MS (Batista et al., 2017; Beatty et al., 2003; Jehna et al., 2011; Krause et al., 2009; Mike et al., 2013; Passamonti et al, 2009). Arguably, among these functional and structural imaging works, five dealt only with the recognition of emotional facial expressions (Batista et al., 2017; Beatty et al., 2003; Jehna et al., 2011; Krause et al., 2009; Passamonti et al, 2009). One of them had no significant outcomes

(Beatty et al., 2003), and one investigating both ToM components involved patients with different MS subtypes and reported no relationship with cognitive ToM (Mike et al., 2013). Structural MRI studies found correlation of emotional recognition with lesions in fiber tracts connecting left temporal WM with orbito-frontal cortex and superior temporal sulcus (Krause 2009); with a reduction in regional cortical thickness (right and left fusiform areas and right entorhinal cortex), with total and regional lesion load of WM fibers and with cortical atrophy of temporal pole, fusiform face area and frontal eye field (Mike et al., 2013); or with more focal atrophy in the amygdala, followed by putamen and numerous cortical fronto-temporal regions (Batista et al., 2017). Structural MRI findings also included: decreased whole-brain and GM volumes in the absence of emotional recognition deficits (Jehna et al., 2011), reduced cortical and deep GM volume (Batista et al., 2017) and decreased cortical thickness in the left anterior inferior temporal gyrus (Mike et al., 2013) in the presence of failed performance. Functional neuroimaging studies reported an association, on the one hand, between a poor recognition of unpleasant emotions and hypoactivation of the superior temporal sulcus, ventrolateral prefrontal cortex and insula (Krause et al., 2009); on the other, between an intact performance and hyperactivation of the ventrolateral prefrontal cortex, precuneus and superior parietal cortex (Passamonti et al., 2009) and of posterior cingulate cortex and precuneus (Jehna et al., 2011).

Taken together, all these findings are not conclusive. First, no neuroimaging study assessed both cognitive and affective ToM, along with other social and non-social aspects of cognition, in a homogeneous group of RRMS patients. Second, there is no consensus on the pattern of ToM impairment in the early stages of MS, particularly if the ability to infer the thoughts and intentions of others is affected as much as emotional recognition. Finally, existing literature on moral cognition in MS is very limited. It is also worth noting that social cognition is, in itself, a heterogeneous concept, which makes studies in this field difficult to compare in terms of focus of investigation (affective or cognitive components), kind of task (e.g., perspective taking versus decoding) and presentation modality of stimuli (verbal or visual).

2.2.3 Disease-related factors and daily living effects

As discussed above, MS is one of the most common neurological diseases with a wide range of personal and social sequels. The disease onset typically occurs at a time when people are making plans for their future, preventing them from being productive in many aspects of their lives. Given the high heterogeneity of MS-related cognitive impairment, it is difficult to delineate a typical clinical profile, but the most considerable negative consequences relate to overall functioning, including mood, fatigue, employment, disability, and quality of life. The existence of links between cognitive, affective and functional changes in MS has been established, but the way these factors interact is not clear.

Mood. Research has shown a relationship between emotional and cognitive symptoms in many neurological disorders, including MS. Major depression is common, with a lifetime prevalence of up to 50%, which is much higher in MS patients aged between 18-45 years (25%) (Feinstein, 2002; Patten et al., 2003). Depression is usually diagnosed early in the course of the disease and is believed to interfere with both cognitive and non-cognitive activities (Feinstein, 2002; Schwid, 2003). The most affected cognitive aspects include working memory, processing speed, learning and memory, abstract reasoning, and executive functions. Although depression has shown to be associated with neuropsychological performance, other investigations have found no relationship between the two (Arnett, 2005; DeLuca et al., 1994; Demaree, Gaudino & DeLuca, 2003; Denney, Sworowski & Lynch, 2005; Feinstein, 2002). However, evidence shows that treated depression can lead to an improvement in cognitive performance (Demaree, Gaudino & DeLuca, 2003). Many studies have reported a relationship between mood and myelin loss, in which demyelination in some brain regions appears to contribute to depression more than other areas. More precisely, it has been suggested that a disconnection between cortico-subcortical areas, which are important for limbic system, caused by lesions in fronto-temporo-parietal WM and independently of neurological disability, as well as atrophy, might contribute to mood disorders in individuals with MS (Berg et al., 2000; Feinstein et al., 2004; Zorzon et al., 2001). A different consideration concerns anxiety, which has been investigated only in a few studies and in combination with depression, and the evidence is conflicting. On the one hand, it has been suggested

that anxiety and depression have an impact in moderating disability and quality of life, on the other, no correlation with MRI abnormalities (brain atrophy or lesion load) or clinical variables have been demonstrated (Janssens, et al., 2003; Zorzon et al., 2001). This lack of a significant association between anxiety symptoms and MRI or clinical data has led to the opinion that anxiety is a reactive response to psychosocial pressure exerted on patients (Zorzon et al., 2001). Recently, data from a systematic review of a large number of patients estimate that the pooled mean prevalence is 30.5% for depression and 22.1% for anxiety, while the prevalence for clinically significant symptoms is 35% and 34% respectively (Boeschoten et al., 2017). However, it is difficult to draw definitive conclusions on the single effect of anxiety, since depression is generally considered to be the most dangerous symptom and therefore taken into greater consideration by clinicians. As a matter of fact, depression is the most frequent sign of psychological distress and is associated with increased suicide rates (1.95% to 18.5%). The presence of depression can reduce adherence to treatment and seriously compromise patient self-care, which makes it very important to actively identify and deal with depressed mood. With their depression treated and cognition improved, patients should be able to cope cognitive difficulties, such as memory loss, which would then help improve general well-being and quality of life (Bradshaw & Rose, 2008; Feinstein et al., 2004; Henze, 2007). Depression and fatigue are also related in MS, as treating one has effects on the other. Interestingly, the treatment of depression (cognitive behavioral therapy, group psychotherapy and anti-depressant therapy) has been shown to decrease the production of the pro-inflammatory cytokine IFN-γ in patients with RRMS (Mohr, Hart & Goldberg, 2003). This finding highlights the need for more research into the potential disease modifying properties associated with the treatment of depression in MS (Bradshaw & Rose, 2008).

Fatigue. Fatigue is a multi-dimensional symptom and is characterized by an overwhelming sense of tiredness, a feeling of complete exhaustion, or a total lack of physical or mental energy, and is often the first noticeable sign that MS individuals experience (Fisk et al., 1994). Fatigue is extremely common in MS (78-91%) to the point that many patients consider it one of the most debilitating aspects of the disease. Fatigue in MS is very different from that experienced by healthy individuals as it has a devastating effect on physical and cognitive functioning, and is known to be exacerbated by heat. Moreover, it can be so severe that it influences work, social relationships, daily mental

and physical activities, and is one of the main reasons cited for unemployment among MS patients. However, fatigue is a subjective symptom that varies from patient to patient and is usually measured with self-report questionnaires rather than objective measures (Bakshi, 2003; Fisk et al., 1994; Johnson, 2008). Since decrements of performance over time in tasks requiring sustained mental effort, such as working memory and vigilance, have been noted, strains to measure fatigue objectively are increasing (DeLuca, 2005). Treating fatigue has shown to alleviate depression and improve cognition. In a study investigating the effects of the wake promoted by modafinil drug in non-MS patients with depression, significant improvements in fatigue and depression were noted, in addition to significant gains in cognition using the Stroop test. These effects in non-MS depressed patients were also hypothesized for depressed MS patients (DeBattista et al., 2004). Another study examined the effect of fatigue management and energy conservation in MS, shortly after attending a course and then seven to nine months later. The total score on the Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) showed significant improvements at both time points. Interestingly, the cognitive subscores of the MFIS were also significantly improved, while depression score decreased significantly to a normal level at the end of training and the two follow-ups. These findings demonstrate that improved fatigue not only has a positive effect on tiredness in MS, but also on cognition and depression (Sauter et al., 2008).

Cognition, depression and fatigue. There is a complex interplay between cognitive impairment, fatigue and depression in MS, all of which are present as a direct result of the disease-related CNS damage (**Figure 6**; Bradshaw & Rose, 2008). Although the etiology of depression in MS remains unclear, it appears to be directly associated with brain lesions and atrophy in specific areas, namely the left anterior temporal/parietal regions. In addition, psychosocial factors, such as disease intrusiveness and burden, may also influence depression in chronic disease. Despite the fact that it is recognized that non-MS people with depression are susceptible to cognitive deficits, most of the early studies showed no correlation between depression and cognitive decline in MS (Siegert & Abernethy, 2005). These works focused on the effect of depression on cognitive performance. Other researchers seem to offer an explanation for these early findings, suggesting that cognitive performance may be unaffected in MS and that demanding aspects of cognition, rather than automatic information processing, are influenced by

moderate or severe depression (Arnett et al., 1999a, 1999b; Arnett, Higginson & Randolph, 2001). Consequently, cognition areas that require attention such as information processing, memory and executive functioning are affected by depression, while performance often remains normal (Siegert & Abernethy, 2005). This hypothesis was also supported by Diamond and colleagues (2008) who showed that slower information processing was related to higher levels of depressed mood. However, according to the authors there must be a significant degree of depression before there is any effect on cognition. A recent, multicenter study by Damjanovic et al. (2017) confirmed these findings in a group of 62 RRMS patients undergoing a neuropsychological test battery and 3D MRI volumetric sequences. While the EDSS score showed a significant correlation with the WM total volume, cognitive performances were related to the GM total volume. A multivariate analysis associated individual brain areas with different cognitive functions. In particular, the volume of the hippocampus was correlated with global cognitive performance, the volume of basal ganglia with attention measures and the overall brain volume with visual memory tasks. An Italian study by Pravatà and coworkers (2017), using morphological MRI sequences, verified the association between brain atrophy and cortical thickness and the presence of cognitive impairment and depression. Their results showed a correlation between depression and atrophy of the orbitofrontal cortex and inferior frontal gyrus. The superior frontal cortex, lateral and medial parietal cortex, temporal, cingulate and entorhinal cortices, thalami, accumbens nuclei, and basal ganglia were predominantly involved in patients who were cognitively impaired. The underlying pathogenesis of fatigue in MS is the least well understood of the neuropsychological symptoms. Fatigue can be caused by the disease process (primary fatigue) or by other problems including insomnia, infections, or psychological reasons, such as coping strategies (secondary fatigue) (Johnson, 2008). Neuroimaging studies suggest that fatigue is associated with brain atrophy and diffuse axonal damage in some patients (Mathiesen et al., 2006; Tartaglia et al., 2004). Recently, morphological alterations and distinct microstructural changes, mainly in the thalamus, but not typical MS lesions, were found to be related to cognitive fatigue in early MS (Wilting et al., 2016). Some evidence that depression has an effect on fatigue in MS is also present. Indeed, a significant correlation between fatigue and mood level has been demonstrated, suggesting that mental rather than physical fatigue is influenced by the presence of

depression. Furthermore, treating depression seems to have a positive effect on subjective measures of fatigue (Ford, Trigwell & Johnson, 1998; Schreurs, de Ridder & Bensing, 2002). As far as the relationship between fatigue and cognitive decline is concerned, this link is less clear even though it is likely to be an interaction between the two symptoms. In particular, there is a strong association between self-reported fatigue and an impairment in subjective, but not objective, measures of cognition. In fact, many patients report that their cognitive performance is reduced by fatigue, but it is also possible that cognitive impairment may increase fatigue (Parmenter, Denney & Lynch, 2003; Winkelmann et al., 2007). Finally, effectively treating fatigue also has a positive effect on depression and cognition (Mohr, Hart & Goldberg, 2003). In short, there is a complex interplay between cognition, depression and fatigue, and each symptom affects negatively the others and dramatically impacts on the social and working lives of MS sufferers. Consequently, it is desirable to identify and treat these symptoms early in the MS course, adopting a multimodal approach that may have a significant effect on the well-being and quality of life of patients.

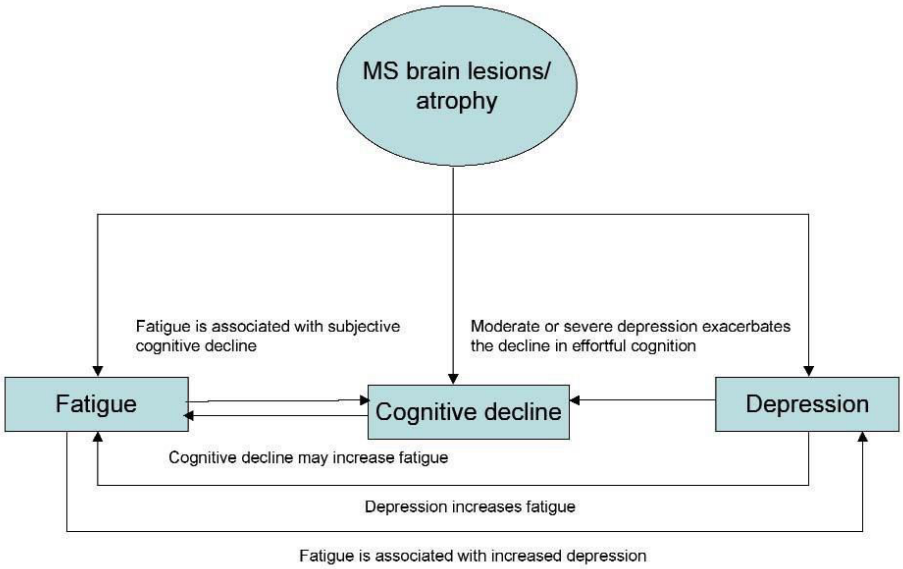

Figure 6. *The interplay between cognitive decline, fatigue and depression*. From Bradshaw & Rose (2008). *Adv Clin Neurosci Rehabil*, **8**(4):15-17.

Employment. Rao and colleagues (1991b) were the first to find that functional status was closely associated with cognitive dysfunction in MS. In their study, cognitively impaired individuals with MS participated in fewer social and vocational activities, were less likely to be employed, had more difficulties in carrying out routine household tasks, and were more vulnerable to psychiatric illness than people with a purely physical disability. The onset of MS, typically occurring in young adulthood, frequently leads to the loss of gainful employment for many patients. Several investigations noted that unemployment affects 40-80% of individuals with MS and occurs in 50-80% of patients within 10 years of disease onset. Cognitive impairment is believed to be the major contributor to this high rate, while physical disability and demographic factors were previously considered as representing less than 14% of the variance in employment status in patients with MS (Beatty et al., 1995; Edgley, Sullivan & Dehoux, 1991; Grønning, Hannisdal & Mellgren, 1990; Rao et al., 1991b). Recent findings underscore the complexity involved in predicting who will and will not maintain full and part-time employment while coping with the physical, cognitive, psychological, and support system challenges of MS. Overall, individuals with lower age at onset, shorter disease duration, higher education, less fatigue and less disability, and greater financial security were more likely to be involved in full or part-time employment (Bøe Lunde et al., 2014; Roessler et al., 2015). Deficits in several cognitive domains were blamed for the difficulty in maintaining employment, in particular, information processing efficiency, memory, and executive dysfunction (Beatty et al., 1995; Parmenter, Shucard & Shucard, 2007). Several works reported that patients with MS have a reduced ability to make decisions that could affect functioning during everyday life, mainly due to deficits in learning of new information regardless of demographic or physical disability variables (Kessler et al., 1992; Nagy et al., 2006). Interestingly, one study showed that processing speed can predict performance in both daily tasks and executive functioning tests. Using a standardized assessment battery designed by occupational therapists, Kalmar and coworkers (2008) found that cognitive performance was correlated with objective assessment of activities during everyday life, whereas subjective assessment of functional activity was related to emotional distress. Although executive function performance did not depend on speed, as patients could take their time, processing speed test was associated with daily life-measures that required speeded responses. Documented

cognitive dysfunction, especially processing speed, verbal memory, and executive functioning, appears to predict vocational status, even after taking into account the effects of age, education, sex, depression, and disease course (Benedict et al., 2006a; Rao et al., 1991b). In general, MS results in considerable breaks in the lives, lifestyles, and occupational status of affected individuals, which have a detrimental effect on personal, professional, and social functioning, thereby affecting overall quality of life. Although physical disability hampers day-to-day activities, it cannot account for the extent of difficulties encountered by individuals with MS for many daily activities, particularly in those requiring substantial cognitive load (Chiaravalloti & DeLuca, 2008).

Clinical variables. As discussed previously, the influence of MS features on cognitive processes is a matter of controversy. The role of disease-related factors, such as duration and severity as well as course of the disease, on cognition has been extensively studied but results are not conclusive due to other important confounding aspects. Correlations between cognitive impairment and indicators of MS progression are inconsistent. In particular, disease duration and cognitive decline do not appear to be directly linked, because once cognitive deficit is established it tends to deteriorate over time, but with specific trend and evolution other than the progression of the disease, in addition to varying considerably between one patient and another (Amato et al., 2010). Similarly, the severity of the disease also shows a non-linear relationship with cognitive impairment. MS disability is usually evaluated with EDSS score, which is an index of global neurological impairment and is universally accepted to measure treatment efficacy. Recently, it has been noted that, as EDSS is primarily driven by motor-walking disability, it is largely insensitive to cognitive deficits. In other words, cognitive functioning does not impact EDSS score as it varies independently of walking ability. Consequently, EDSS is insensitive to assessing individual MS cognitive impairment and is not able to predict accumulated cognitive disability (Gudesblatt et al., 2016). Most research in MS supports the concept that cognitive impairment is progressive with some evidence of stability or improvement once appeared. Although disease duration and physical disability do not predict cognitive impairment, there is a likely relationship with disease subtype and time since diagnosis (DeLuca et al., 2015). In a 3-year follow-up study, it was found that the majority of subjects who were initially cognitively intact remained stable at the end of the study, whereas 77% of impaired patients at the baseline showed significant

deterioration especially in memory and processing speed (Kujala, Portin & Ruutiainen, 1997). In a large cross-sectional study in which subjects were divided in 5-year cohorts by year of diagnosis, Achiron and colleagues (2005) found a pattern of cognitive decline after the fifth year after diagnosis, characterized by a decreased visuospatial learning and memory, attention and processing speed. Cognitive impairment was also more frequent and severe in progressive courses than RRMS. In their 2-year study of PPMS, Camp et al. (2005) observed a considerable variability in their sample. While in terms of individual variations, 37% of patients showed a significant cognitive decline, mean perfomance had not significantly changed, with some patients getting worse and others remaing stable or showing improvement. In a long-term, controlled study, Amato and coworkers (1995, 2001) compared 50 early-onset MS subjects with 70 healthy controls at 4- and 10-year follow-ups. At the beginning, 74% of MS patients were cognitively intact and 88% were in RR course (1.5 years since diagnosis and 1.8 EDSS mean score). Impaired verbal memory and abstract reasoning were seen at the baseline, difficulties in verbal comprehension and memory emerged after 4.5 years, and additional deficits in short-term verbal and spatial memories were found at the end of the study. Although disease progression and severity and cognitive outcome tended to converge at least in the long-term, after 10 years most patients were not cognitively impaired and no feature was found to be predictive of worsening compared to cognitive dysfunction at the baseline. Similar findings were observed in another 10-year-follow-up study, in which 27-44% of patients showed a decline over time in working memory and processing speed, but no significant changes in memory and semantic retrieval were seen (Schwid et al., 2007). Taken as a whole, available evidence suggests that MS-related cognitive outcome may be heterogeneous, but once cognitive dysfunction is established it tends to persist. It can also remain stable for years, but after a sufficient long follow-up period it tends to progress even if at different rates, frequency and severity. Another confounding factor about MS would be the disease course. Since SP patients have a prior history of relapsing disease that has subsequently evolved in a progressive course, SPMS can therefore be considered a more advanced stage of MS, which could be expected with greater cognitive impairment. Conversely, individuals with PPMS have no history of relapsing disease and therefore a comparison between them and RR patients does not necessarily imply a difference in chronicity. Unfortunately, research on this topic was controversial, as the

effect of disease course could be confused with several other variables, such as age, disability, and duration of illness (Amato et al., 2010). Despite the potential confounders, only a few studies investigated the differences in cognitive abilities among MS patients with PP, SP and RR subtypes, and as such results appear heterogeneous (de Sonneville et al., 2002; Denney, Sworowski & Lynch, 2005; Gaudino et al., 2001; Huijbregts et al., 2004; Planche et al., 2016; Potagas et al., 2008). The more common practice was to compare people with relapsing and chronic progressive courses, combining both PP and SP patients in the latter group. Typically, patients with chronic-progressive MS were found to have more pronounced impairment than those with relapsing disease (Denney, Sworowski & Lynch, 2005). In the few cases where PPMS and SPMS were distinguished, some researchers found greater cognitive impairment in SPMS (Comi et al., 1995; Gaudino et al., 2001; Huijbregts et al., 2004; Planche et al., 2016; Ruet et a., 2013), while others reported essentially no difference between these two progressive forms (de Sonneville et al., 2002; Foong et al., 2000; Potagas et al., 2008). A meta-analytic study found that distinct patterns of neurocognitive deficits were evident in chronic-progressive and relapsing subtypes of MS, and these differences were not only found in the magnitude of deficit, but also in the pattern of cognitive dysfunction. According to the authors, patients with chronic-progressive MS had a greater tendency for demyelinating lesions affecting frontal structures and therefore presented a more frontal-executive impairment, while patients with RRMS had a more memory-related dysfunction. In other words, these differences in magnitude of deficits, but not in pattern, would suggest a similar distribution of WM pathophysiology among subtypes, but an exacerbated clinical course in patients with chronic-progressive MS. Furthermore, these findings may account for why a considerable number of patients cannot be distinguished from controls on many cognitive tests in primary studies of MS (Zakzanis, 2000). A recent work by Planche and colleagues (2016), comparing 101 MS individuals with PPMS, SPMS and late RRMS (LRRMS), i.e. with disease duration of more than 10 years, showed that 63% of patients had a significant cognitive impairment. After controlling for age, sex, EDSS, disease duration and education level, patients with SPMS were at least 2-fold more frequently impaired than those with LRRMS in information processing speed, executive functions, verbal fluency, verbal episodic memory, working memory and visuospatial ability. These results were quite similar when comparing the PPMS and LRRMS groups, but patients

with PPMS were more frequently impaired in verbal fluency and more often had at least one impaired cognitive domain. SPMS and PPMS groups showed a similar cognitive profile, but SPMS patients were more often compromised in visuospatial construction. Altogether, these findings demonstrated that cognitive impairment in MS patients with progressive forms was wider and more frequent than those with a relapsing course, even after more than 10 years of disease. Apart from visuospatial ability, the cognitive profile was the same regardless of the disease subtype, and the difference between LRRMS, PPMS and SPMS was therefore much more quantitative than qualitative.

Quality of life. As a multidimensional construct, quality of life consists of at least three general domains; i.e. physical, mental and social. In the field of medicine, researchers and clinicians have often used health-related quality of life (HRQoL) concept, which specifically focuses on the impact of an illness and/or treatment on patients' perception of their health status and on subjective well-being or satisfaction with life (Jaracz & Kozubski, 2003). As noted above, impaired cognition, reduced fulfilment in work life and social life may subsequently result in a poor quality of life (Bradshaw & Rose, 2008; Rao et al., 1991b). Nevertheless, existing studies have revealed contradictory results about the relationship between cognitive functioning and quality of life. The potential weaknesses of these studies may concern the measures chosen to evaluate such variables (Baumstarck-Barrau et al., 2011). Most evidence suggests non-significant trends between cognitive status and quality of life (Amato et al., 2001; Baumstarck-Barrau et al., 2011; Benedict, et al., 2005; Lovera, et al., 2006; Rao et al., 1991b). Besides, when an association was found, the assessment was restricted to a single cognitive domain (Gold et al., 2003; Miller et al., 2000), or included tools recognized as insufficiently sensitive (Benito-Leon, Morales & Rivera-Navarro, 2002; Montel & Bungener, 2007), or quality of life predictors were not considered simultaneously (Miller et al., 2000; Montel & Bungener, 2007). Even existing data regarding factors that predict quality of life in MS population are somewhat contradictory. For example, in some cases gender was not reported as relevant for the global quality of life (Benedict, et al., 2005; Benito-Leon, Morales & Rivera-Navarro, 2002), while other authors found that men showed a better quality of life than their female counterparts (Hopman et al., 2009). Women reported a worse quality of life than men in terms of coping and rejection, suggesting that they may be more vulnerable in these dimensions. On the other hand, women had a higher quality

of life in relationships with friends and sentimental life (Pekmezovic et al., 2007). Regarding the disability level, the direction of this effect also varies. In some cases, high disability was related to poorer quality of life related to activities of daily living (Benedict, et al., 2005). Conversely, severe disability was associated with better global quality of life and higher scores in the psychological well-being and healthcare dimensions, suggesting the potential relevance of coping strategies (McCabe, Stokes & McDonald, 2009). Instead, the influence of depression and fatigue as independent predictors of some aspects of quality of life in MS patients appears to be confirmed (Lovera, et al., 2006; Mitchell et al., 2005). While EDSS scale is more a predictive index of the global and physical quality-of-life domains, depression scores relate to more general contentment and global quality of life (Fernández-Jiménez & Arnett, 2015). Combination of relapses, disease activity and progression on MRI is another important part of the impact that MS has on a patient's daily life. HRQoL represents the link between quality of life and individual health status, such that a recent relapse could transiently modify HRQoL perception. Despite the controversial associations between EDSS score and MRI outcome, patients also consider physical function (58%) and role limitation (46%) as important aspects of their HRQoL (Ysrraelit et al., 2018). Various regional MRI abnormalities have been associated with impaired quality of life in patients with MS in multiple HRQOoL domains (Janardhan & Bakshi, 2000). In particular, regional WM lesions and atrophy (temporal and occipital lobes, lateral ventricular bodies enlargement, pons, superior and inferior parietal lobe) showed a significant relationship with worsening in sexual dysfunction, role limitations due to physical and/or emotional dysfunction, and overall mental health. However, overall physical health was not found to be related to any brain MRI abnormality. These weak and contradictory relationships on predictors of quality of life confirm that clinical assessment does not reflect all the aspects that patients consider important in their lives. Since quality of life is a subjective measure of well-being and satisfaction for life, the extent to which an individual perceives a good quality of life depends on many factors: experienced cognitive problems, depressive symptoms, physical disability and disease progression, cerebral activity on MRI, concerns about disease consequences, coping strategies, and so forth. All these parameters may be of significant clinical value for MS healthcare, reminding the need to use a multidimensional approach for quality of life assessment (Baumstarck-Barrau et al., 2011).

Rehabilitation

It is well established that cognitive deficits in MS patients have a negative effect on their personal, occupational and social lives (Shevil & Finlayson, 2006). Some studies have provided evidence on the positive effect of cognitive rehabilitation on mood, fatigue, quality of life, and subjectively experienced effects of cognitive problems (Brenk, Laun & Haase, 2008; Rosti-Otajärvi & Hämäläinen, 2014; Stuifbergen et al., 2012; Vogt, et al., 2009), while different findings have been reported by other authors (Hildebrandt et al., 2007; Shatil et al., 2010; Tesar, Bandion & Baumhackl, 2005).

Vogt et al. (2009) suggested that the most important finding in their study was a significant decrease in self-reported fatigue, although depression and self-reported quality of life revealed no significant treatment effect. In a recent paper, Hanssen and colleagues (2016) investigated the effects of cognitive rehabilitation on cognitive and executive coping, psychological well-being and psychological aspects of HRQoL in people with MS. In addition to better executive skills found in both groups of patients, improvements in psychological well-being and psychological aspects of HRQoL occurred from baseline to 4- and 7-month follow-ups only in the intervention group, suggesting that multicomponent cognitive rehabilitation is useful when administered within the context of multidisciplinary rehabilitation. In a similar Italian contribution, Grasso and coworkers (2017) evaluated the effectiveness of cognitive rehabilitation plus multidisciplinary approach versus treatment with multidisciplinary rehabilitation alone over a three-month-period in a group of people with MS. The intervention group showed significantly better executive functioning skills and marked improvement in quality of life, while patients treated with multidisciplinary rehabilitation alone improved only in the physical composite score. Both groups also showed better gains on the depression scale, but this improvement was detected at six months of follow-up only in patients treated with multidisciplinary rehabilitation plus cognitive training. Even this study indicates that multidisciplinary approach is the best treatment that can be used in MS and that cognitive rehabilitation is an important aspect of this program insofar as it improves the quality of life of these patients.

Mixed findings reported by other authors are probably due to several factors, including the difference in the type of cognitive rehabilitation treatment, the inclusion and exclusion criteria used, and in particular the choice of outcome measures, such as

quality-of-life dimension that may take longer periods of intervention to achieve measurable change (Mitolo et al., 2015). Despite this, rehabilitation appears to be a key component of global care and management of people suffering from MS.

2.3 Neuroimaging in MS

2.3.1 Nuclear Magnetic Resonance

Nuclear Magnetic Resonance (NMR) is the gold standard in both clinical practice and research of MS. This structural neuroimaging technique allows the detection of brain atrophy, number and distribution of lesions in the cerebral and spinal parenchyma, and if some of these lesions are in active inflammatory phase by adding the Gd contrast medium (DeLuca et al., 2015; Filippi et al., 2010).

Atrophy measures rely on the precise quantification of the volume, or change in volume, of relevant structures, which can be seen with good contrast, that is, a difference in brightness between tissues that exceeds the level of noise. The size in which scanned objects are displayed is controlled by the accurate calibration of the magnetic field gradients used to encode spatial information. Contrast in the images is influenced by the radiofrequency pulse vibration angles used to create the signal, indirectly affecting atrophy measures since tissue compartments (CSF, GM, WM) are assigned based on their relative brightness in the image. Raw volumes usually need to be scaled to remove confounding factors that affect volume, providing an index of atrophy that can be compared to normative data. One example is the so-called brain parenchymal fraction (BPF), which is the ratio of the brain volume to the intracranial volume. When follow-up scans of the same patient are acquired, volume changes can be quantified with respect to a baseline scan (Rocca et al., 2015). In people with MS, brain atrophy progresses at a rate of approximately 0.5-1.0% per year compared with 0.2-0.4% in healthy individuals (Barkhof et al., 2009; Simon, 2006). Recently, a consensus-based group has established the Percentage Brain Volume Change (PBVC) as a parameter to assess the significance of atrophy in MS patients, indicating that a PBVC cut-off of -0.4% could discriminate the presence or absence of pathological brain volume loss with high specificity (80%) and

good sensitivity (65%) (De Stefano et al., 2016). There are several widely used, freely available software, combining lesion segmentation, registrations, and tissue/structure segmentation. The target anatomy of each tool indicates which parts of the brain it examines (e.g., cortex or deep GM), the measure specifies which aspect of the target anatomy is quantified (e.g., volume or thickness) and whether it is done globally or locally. Global measures often benefit from averaging over a larger volume and can have greater precision and statistical power, while local measurements more richly describe the anatomical changes and are not diluted by areas where there is little or no change. Previous information is often required when performing segmentation and is usually provided via registration to an atlas. Since volumes and thicknesses of brain tissue structures are related to head size, it is common practice to produce normalized values. Normalization factors are often based on automated measurements of intracranial volume or on scaling factors from skull-based or whole-head-based registration to a standard template. For longitudinal assessment of atrophy, tools are normally designed and optimized to work specifically with pairs of images from each participant, because they achieve greater precision than registration to an atlas (Rocca et al., 2015).

Classically, it was thought that MS was characterized since its onset by a focal WM damage observed with typical hyperintense T2-weighted lesions, which sometimes evolved into areas of focal brain atrophy (so-called 'black holes' seen in hypointense T1-weighted sequences). In recent years, it has been observed that a loss of brain volume in MS is also caused by widespread damage of GM and NAWM. Initially, atrophy was evaluated manually by coarse parameters such as total brain volume, corpus callosum thickness, distance between the caudate nuclei (bicaudate ratio), and the width of the third ventricle. These findings on the role of neurodegeneration in MS have led to the study of brain volume by NMR and the development of new methods to quantify it which are constantly evolving. Brain atrophy is mostly measured from T1-weighted images. T2-FLAIR contrast can be utilized for BPF. High-resolution 3-dimensional (3D) acquisition allows the assessment of smaller and thinner structures, and can minimize the reduction in quality when co-registering serial scans. Measurement of atrophy progression also provides clinically relevant information. For instance, ventricular enlargement is more pronounced in patients with CIS who evolve to MS; increased brain atrophy develops in patients with worsening disability than in those who are clinically stable; whole brain

atrophy is related to cognitive dysfunction and mood disorders; and finally, brain volume quantification on early scans provides prognostic measures of clinical status not only for medium and long-term follow-up, but also for short-term (over 6 months) decline (Rocca et al., 2015).

2.3.2 Conventional and advanced techniques

Due to their ability to detect MS-related abnormalities, MRI is the most used paraclinical tool to investigate in vivo the pathobiology and to monitor the evolution of the disease (Filippi et al., 2010). Conventional and quantitative magnetic resonance techniques have hence become a key element of diagnosis and care in MS, also for their contribution to improve understanding of the factors associated with cognitive impairment. Several measures used to capture brain integrity have included whole brain atrophy, cortical atrophy and lesion volume.

Studies on individuals with MS have found only a modest association between T2 lesion burden in the whole brain or in specific WM sites and neuropsychological test performance. This supported the early notion of a functional disconnection between cortical and deep GM structures secondary to WM damage (Filippi et al., 2010). The assessment of T1 hypointensities, which reflect changes in the extent of demyelination and axonal density, has not substantially improved clinico-radiological associations, whereas the quantification of volume decrease (atrophy) of the whole brain or of selected brain regions (i.e., third ventricle, corpus callosum, bicaudate ratio) has provided strong correlates of MS-associated cognitive dysfunction (Houtchens et al., 2007). These measures of brain atrophy are thought to be markers of the most destructive aspects of MS pathology, as they are better correlated than T2 and T1 lesion volumes, both in cross-sectional and longitudinal studies (Rovaris, Comi & Filippi, 2006; Zivadinov et al., 2001). Subsequently, GM involvement in MS has received increasing interest. Evaluation of GM atrophy and topographic distribution of such damage can help to differentiate cognitively impaired from cognitively preserved patients. Interestingly, the GM atrophy rate seems to accelerate around the conversion point from RR to SP phase of MS (Fisher et al., 2008). The effect of focal GM lesions on the development of atrophy or of cognitive impairment

has been difficult to investigate, but with the introduction of new imaging techniques, such as double inversion recovery (DIR) and phase-sensitive inversion recovery, an improved visualization of MS cortical lesions has been achieved. Unlike the T2 hyperintense WM lesion volume and contrast-enhancing WM lesion number, an increase of cortical lesions and atrophy over time can independently predict cognitive impairment (Calabrese et al., 2009; Roosendaal et al., 2009b).

More recently, high-resolution 3D sequences have been introduced and used to maximize the ability to assess cerebral integrity in MS, including Magnetization Transfer Ratio (MTR), Magnetic Resonance Spectroscopy (MRS) and Diffusion Tensor Imaging (DTI). MTRs, measuring the signal intensity with and without application of off-resonance radio-frequency pulses, can be used to detect changes in the structural status of brain parenchyma that are not always visible with standard MR techniques. Use of MTRs may allow sub-categorization of MS lesions into those with very low MTR (demyelinated lesions) and slightly decreased MTR (edematous lesions). Measures derived from MTR have consistently been shown to be associated with cognition, including cortical and subcortical regions, normal-appearing brain tissue on conventional imaging (e.g., thalamus) and NAWM (Deloire, Salort & Bonnet, 2005; Francis et al., 2013; Zivadinov et al., 2001). MRS integrates MRI as a non-invasive means for the characterization of brain tissue and provides a measure of metabolic changes in the WM and cerebral cortex, using the proton signal to determine the concentration of brain metabolites which represent potential surrogate markers for pathology underlying MS. MRS is also a sensitive indicator of cognitive functioning in MS, particularly in NAWM, and its derived measures can be used to distinguish between patients with and without cognitive impairment (Mathiesen et al., 2006; Staffen et al., 2005). Specifically, it was found that the decrease in N-acetylaspartate, a marker of neuronal and axonal integrity, measured in frontal regions, is related to a poor performance in executive functions. Therefore, MRS is a unique tool to follow MS disease evolution: understanding its pathogenesis, assessing the disease severity, establishing a prognosis, and evaluating therapeutic intervention efficacy (Sajja, Wolinsky & Narayana, 2009). DTI has emerged as a key MRI methodology for understanding WM pathology in MS (Rovaris et al., 2005). Fractional anisotropy, reflecting the degree of fiber alignment and integrity, and mean diffusivity, measuring the average molecular motion independent of any tissue

directionality, are the commonly used measures of diffusion. Studies have consistently reported differences in DTI metrics between MS patients and controls within the NAWM (Dineen et al., 2009; Genova et al., 2013; Mazerolle et al., 2013; Roosendaal et al., 2009a; Yu et al., 2012). These abnormalities, reflecting decreased integrity of WM tracts, have been found to predict processing speed deficits, with the strongest correlations observed for SDMT (Mazerolle et al., 2013; Yu et al., 2012). Other studies have also observed a relationship between impaired attention, working memory and processing speed and decreased fractional anisotropy in the corpus callosum and other tracts mainly connecting prefrontal cortical regions. Fiber abnormalities overlap only partially with lesion location, highlighting the importance of lesion-independent NAWM abnormalities in cognition. These studies support the notion of a relationship between damage to specific pathways and related cognitive domains (Dineen et al., 2009; Roosendaal et al., 2009b).

Since the brain cortical reorganization in different stages of the disease might play a relevant role in explaining inter-individual heterogeneity, many important results have been achieved by advanced functional neuroimaging techniques (Filippi et al., 2010). Early studies using positron emission tomography and computerized tomography with single photon emission showed decreased blood flow and oxygenation, especially in frontal cortex and basal ganglia, and a correlation between these changes and cognitive dysfunction in individuals with MS (Blinkenberg et al., 2000; Paulesu et al., 1996; Pozzilli et al., 1991). Taking advantages of nuclear medicine imaging techniques by measuring changes of deoxyhemoglobin concentration, fMRI provided a thorough understanding of brain-behavior relationships and the role of brain reorganization in limiting the cognitive impact of MS-related tissue damage. Nevertheless, the interpretation of results should be done with caution, since fMRI is not based on direct measurement of neural activity, but on a cascade of physiological events that can be influenced by several factors, including regional alterations of the BOLD response and differences in patient and control performance. Functional neuroimaging studies investigating cognitive processes in MS have focused on three main domains, namely working memory, attention and executive functions (Chiaravalloti & DeLuca, 2008; Filippi et al., 2010). Using different cognitive paradigms, fMRI changes were applied to all major clinical phenotypes of the disease. Overall, these abnormalities are characterized by two main patterns of functional cerebral activity during cognitive functioning. First,

the blood-oxygenation-level-dependent responses are frequently observed in people with MS in regions where no activation in normal controls is found. Second, cortical activation areas are largely similar between MS and healthy subjects, but activation levels can be different in MS individuals. There is a bilateral activation of the same areas in cognitively preserved patients, on one side, and a significantly lower recruitment in cognitively impaired patients, on the other (Audoin et al., 2005; Mainero et al., 2004; Penner et al., 2003; Rocca et al., 2009). Several explanations have been suggested, such as cerebral reorganization and recruitment of other cortical regions as a compensatory mechanism. The correlation found in most studies between fMRI activations and structural MRI measures of disease burden, in terms of macroscopic lesions and damage to NAWM and GM, suggested that these fMRI abnormalities could play an adaptive role in limiting the clinical consequences of widespread disease-related damage. This is also supported by the observation that patients with early MS showed greater activation of the dorsolateral prefrontal cortex over one-year, which was associated with improved working memory and processing speed (Audoin et al., 2005, 2008; Bobholz et al., 2006). Task difficulty has also been suggested to explain these findings. In particular, activation patterns seen in MS could be caused by recruitment of additional cerebral resources when the task requires a certain threshold to be reached, probably based on the individual difficulty of the task (Hillary, 2008). Another explanation concerns the observation that neuronal integrity may also affect activation patterns, either directly or indirectly, observed in functional neuroimaging studies. More precisely, by combining measures of abnormal structural and functional connectivity, a selective adaptive response to the damage of WM fiber bundles was demonstrated. For instance, it was observed that RRMS patients with low fractional anisotropy of the superior longitudinal fasciculus experienced a more bilateral cortical activation during PASAT performance than healthy controls (Bonzano et al., 2009). In another study, a correlation between diffusivity changes of the corpus callosum and an abnormal inter-hemispheric connectivity during attention tasks was found, suggesting that a disconnection between brain areas may play a role in the pathophysiology of cognitive impairment in MS (Rocca et al., 2009).

2.4 MRI and cognitive impairment

Given the negative neurological and psychosocial impact of MS, important advances have been made in attempting to relate behavioral disturbances to structural involvement. Currently, MRI is the best biomarker available for both diagnosis and monitoring of disease activity in MS patients.

Recent studies have helped to shed some light on the possible neuroanatomical substrate of cognitive impairment in MS and to interpret MRI findings. From a pathological point of view, MS lesions are heterogeneous even within a given anatomical location, and their distribution and size are highly variable among patients. Each lesion may have an impact on cognition through various mechanisms including chronic inflammation and/or demyelination, axonal loss, oxidative stress, BBB breakdown, and so forth, resulting in changes in cortico-cortical and cortico-subcortical connectivity. Nevertheless, the relationship between MS pathology and cognition remains poorly understood (DeLuca et al., 2015).

MS pathology is multifaceted affecting cortical, deep GM and WM structures. Within WM lesions, there is a loss of myelin, OGCs and axons, while atrophy of NAWM is likely secondary to myelin and axonal damage. GM demyelination is common in neocortical areas, but is also found in other regions, such as the thalamus, hippocampus, and cerebellum. Given the intricate connectivity of these structures, it is likely that each contributes uniquely and additively to MS-related cognitive impairment (Rocca et al., 2017). Further, a recent post-mortem study, investigating two thalamo-cortical projection systems, namely lateral geniculate nucleus to primary visual cortex and mediodorsal nucleus to prefrontal cortex, suggested that pathology of one structure may affect the pathology in the other. The authors demonstrated that total lesion burden affecting the connecting WM structures was not associated with the severity of pathology within each of the thalamo-cortical projection system studied. Their findings have shown that nerve cell or axonal loss in a specific brain area can lead to anterograde or retrograde degeneration in connected brain regions (Kolasinski et al., 2012). These neurodegeneration events are known to trigger microglial activation in areas distant from the initial lesion which, in turn, propagates an inflammatory cascade leading to free radical generation and oxidative stress, and hence neuronal-axonal demise (Lassmann,

2012). If these traits were to be involved in cognition, as in the case of the dorsomedial thalamic and prefrontal circuit, a cognitive decline should be expected. In other words, in the early disease stages in which inflammatory demyelination is predominant, GM and WM lesions may disrupt thalamic pathways relevant for cognition, including dorsolateral prefrontal cortex (e.g., working memory, planning, and cognitive flexibility), orbitofrontal cortex (e.g., decision making and adaptive learning), posterior parietal cortex (e.g., spatial memory and attention), and anterior inferior temporal cortex (e.g., semantic memory) (DeLuca et al., 2015). Moreover, the initial predominant WM pathology could lead to subtle changes in subcortical cognitive functions often encountered early on, such as psychomotor slowing and inattention. As the disease progresses, diffuse cortical and WM pathology may overwhelm the focal inflammatory demyelinating lesions leading to cognitive deficits typical of degenerative dementias, such as aphasia, apraxia and agnosia (Kutzelnigg et al., 2005; Querfurth & LaFerla, 2010). Clearly, if cognitive dysfunction is a manifest clinical symptom of MS, early disruption of interconnected cognitive pathways remains the main suspect (Lucchinetti et al., 2011).

2.4.1 MS pathology, neuroimaging and cognition

2.4.1.1 White matter

Impaired processing speed is the most common deficit observed in MS and appears to be heavily dependent on WM integrity. Even if MS-related diffuse lesions are evident in WM, any sort of focal or widespread brain injury can affect processing speed, as it depends on basic neuronal function and glial support. Because of its diffusivity, no brain areas have shown to be necessary for processing speed, outside of global WM (Viana-Baptista et al., 2008).

There is a spectrum of WM abnormalities recognized in MS, ranging from lesional acute and chronic WM, diffusely abnormal or dirty appearing WM (DAWM) and NAWM. WM lesions have long been considered the pathological hallmark of MS and can be detected both in vivo by MRI and post-mortem investigations. Furthermore, acute demyelination is widely accepted as the pathological surrogate for clinical relapses,

demonstrated by MRI evidence of Gd enhancement. Re-myelination of WM lesions is highly variable between patients and within lesions of the same patient and is inefficient compared with that observed in cortical GM. Myelin deposited from re-myelination is susceptible to second-attack demyelination, and the resulting disruption of WM fiber bundles has a deleterious impact on cognition. While WM lesions can occur anywhere, their distribution is not random, with periventricular, centrum semiovale and corpus callosum involvement being common (Bramow et al., 2010; Kolasinski et al., 2012; Lassmann, 2011; Patrikios et al., 2006).

Outside of lesions, in MS the myelin of WM typically displays pathological changes ranging from NAWM to DAWM. NAWM is different from WM in control tissue due to diffuse parenchymal and perivascular T-cell inflammation, microglial activation and BBB permeability (Dutta & Trapp, 2011). NAWM abnormalities defined on MRI correlate with atrophy, disability and impaired cognition, compared to lesion burden. DAWM refers to WM myelin with hyperintensity on T2-weighted imaging, intermediate between that of NAWM and focal WM lesions. Typical locations are adjacent to periventricular plaques and occipital WM, although they can affect any part of WM including areas distant to lesions (Moore & Laule, 2012; Moore et al., 2008). Axonal injury and loss are established features of MS WM pathology and likely contribute significantly to the irreversible cognitive decline often seen in the disease. Atrophy in WM is observed in both demyelinating lesions and NAWM. In the first case, the presence of axonal loss is associated with myelin and OGC damage, while in both NAWM and DAWM it can be partly explained by secondary Wallerian degeneration stemming from acute lesions in structures such as the corpus callosum (Evangelou et al., 2000; Tallantyre et al., 2010).

Demyelinating plaques, both active and chronic, are seen as high signal on T2 MRI sequences. These hyperintense T2 lesions are related to cognitive impairment and have been found to better correlate than T1 or Gd+ lesions (Deloire, Salort & Bonnet, 2005). Rossi and colleagues (2012) reported greater WM lesion volume in MS patients who were cognitively impaired than those who were preserved, noting that the peak of lesion frequency was two times higher in the corpus callosum. The authors also found that low SDMT scores were significantly associated with high lesion frequency in this area.

As noted, more interesting contributions come from studies using new advanced neuroimaging techniques, either alone or with other tools. In accordance with the previously discussed, the best marker for WM integrity, such as NAWM abnormalities, remains the DTI (Dineen et al., 2009; Roosendaal et al., 2009a; Rovaris et al., 2005). Of the three classically recognized cortico-striato-thalamo-cortical loops involved in cognitive and emotional processes rather than in basic motor ones (Alexander, DeLong & Strick, 1986), the dorsolateral prefrontal cortex circuit appears to be most correlated with processing speed as well as with executive functioning (DeLuca et al., 2015). Although they share the same circuits, processing speed is much more globalized and many brain structures or areas may affect it.

2.4.1.2 Cortical gray matter

The ability to separately analyze the contribution of GM and WM has been one of the major advances in quantification of atrophy and, despite the involvement of both compartments, GM atrophy provides most clinically relevant information (Rocca et al, 2017). The combination of application of immunohistochemistry, increased awareness of cognitive dysfunction in MS and its relationship to GM structural change on MRI have shifted the WM-centric view to the role of cortical GM pathology in the pathogenesis and phenotypic expression of the disease (DeLuca et al., 2015).

Cerebral cortex is surrounded by a complex network of glial cells, myelin and extracellular matrix proteins. Disruption of these neuronal connections represents the substrate for several neuropsychiatric conditions, many of which have cognitive dysfunction as a core feature, and it is therefore possible that similar processes are involved in MS-related cognitive impairment (DeLuca et al., 2015).

Recently, advanced MRI techniques, such as DIR sequences, have shown that cognitively impaired MS patients have a significantly higher cortical lesion volume and lower overall cortical volume, which are independent predictors of cognitive impairment (Calabrese et al., 2009). Studies using BPF index to quantify the amount of atrophy have reported that this parameter better correlated with clinical variables, such as disease duration and severity as measured by EDSS, than the number of T2 lesions, suggesting that atrophy is a measure of degeneration or permanent damage (Chard et al., 2002; Fisher

et al., 2000; Horsfield et al., 2003; Kassubek et al., 2003). Although both GM and WM atrophy are noted over time, MRI evidence supports GM atrophy as the driving force behind whole brain atrophy. While WM atrophy was found at a similar rate in all MS types, i.e. 3 times greater than normal controls, GM atrophy occurred 8.1 times higher in RRMS, 12.4 in RRMS converting to SPMS and 14 in SPMS patients (Benedict et al., 2004; Chard et al., 2002). A similar relationship has been described between atrophy measures and cognitive functions. It was shown that MS patients who are cognitively impaired have smaller overall brain, GM and WM volumes, and BPF index is correlated with processing speed (Benedict et al., 2004; Lazeron et al., 2006; Sanfilipo et al., 2006). Moreover, Amato and colleagues (2004), examining 41 MS patients within 10 years of diagnosis, found that MS group compared with healthy subjects has a decreased neocortical volume, and the same is true for cognitively impaired patients compared with those without cognitive impairment. In that study, neocortical volume was significantly correlated with measures of auditory and verbal memory, attention, and verbal fluency, also demonstrating a reationship between neocortical atrophy and cognitive speed (**Table 2**). Hence, it may be argued that there is a threshold of cerebral tolerance that must be trespassed before cognitive disturbances achieve clinical relevance.

Region	Subregiorn	Anatomic structure	Cognitive function
White matter	Subcortical WM	N/A	Processing speed
Gray matter	Cortical GM	Cerebral cortex	Processing speed; Memory; Verbal fluency
		Hippocampus	Memory
	Deep GM	Thalamus	Processing speed; Memory; Verbal fluency; Working-memory; Executive functions
		Basal ganglia	Memory; Verbal fluency

Table 2. *Affected cognitive abilities featured by anatomical location in MS*. Adapted from Amato et al. (2004). *Neurology*, **63**(1):89-93; DeLuca et al. (2015). *Brain Pathol*, **25**(1):79-98.

Cortical demyelination may occur at an early stage of the disease and has been documented in all clinical phenotypes, being most prevalent and widespread with advanced disease duration and in progressive course (Kutzelnigg et al., 2005; Lucchinetti et al., 2011). Cortical regions particularly prone to demyelination include the cingulate gyrus, temporal and frontal cortices, and the depths of sulci, while the paracentral lobule, occipital lobe and primary motor cortex display a relatively minor amount of pathology. That being said, no cortical region is universally spared from the MS disease process and, in fact, in the progressive phase, most of the cortical ribbon can be demyelinated, although this can vary considerably among patients (Gilmore et al., 2009; Kutzelnigg et al., 2005). Cortical demyelination is not a permanent outcome in MS and increasing evidence suggests that cortical re-myelination is frequent and can be extensive compared to that of WM (Chang et al., 2012). The relationship between the extent of cerebral cortical re-myelination and age is controversial. On the one hand, recent works have demonstrated that MS cases with longer disease duration and older age at death had more abundant cortical myelination, suggesting that likely re-myelination extends into old age and may contribute to 'cognitive reserve' (Patrikios et al., 2006; Yates et al., 2015). On the other hand, since evidence indicates that OGC re-myelinating potential decreases with age, this phenomenon would be influenced by the changing inflammatory activity associated with aging, which could subsequently impact the susceptibility of newly formed myelin from 'second-hit' demyelinating attack in older patients (Bramow et al., 2010; Goldschmidt et al., 2009). Overall, the observed substantial inter-individual variation in re-myelinating capacity regardless of age suggests underlying genetic and/or environmental factors.

Atrophy of selected GM regions can explain specific clinical deficits or variability among different disease courses. The preferential susceptibility of prefrontal, middle temporal and cingulate cortices to demyelination probably contributes to deficits in executive functions, learning, memory retrieval, emotion formation and processing often encountered in the disease (DeLuca et al., 2015). A well-characterized pattern of regional GM atrophy involving several frontal, parietal, and temporal regions has been proposed by Riccitelli and colleagues (2011) and distinguishes between cognitively impaired and preserved MS subjects according to clinical phenotypes (**Figure 7**). Distinct patterns of regional distribution of GM damage were associated with cognitive impairment in MS patients with different phenotypes. While subjects with RRMS had a prominent

involvement of deep GM structures (thalami, insula, superior temporal gyrus, and middle occipital gyrus), patients with progressive MS courses exhibited GM loss in cortical regions, which are functionally relevant for cognitive processing. Moreover, there were no regions significantly more atrophied in cognitively impaired SP subjects compared to RR patients, suggesting that RRMS and SPMS represent a *continuum* of the same process, whereas different pathological mechanisms might be in PPMS. Conversely, compared with PPMS (anterior cingulate cortex and right superior temporal gyrus), cognitively impaired SPMS patients had a significant GM loss in several regions of the fronto-temporal lobes (orbital gyri, anterior cingulate cortex, right middle frontal gyrus, middle occipital gyrus, hippocampi, insulae, right superior temporal gyrus, and right superior frontal sulcus), the left hypothalamus and thalami. In summary, the observation that a significant atrophy in several cortical regions in the frontal, parietal and temporal lobes as well as in several deep GM structures, was found in MS patients with cognitive impairment compared with those cognitively preserved and controls, supports the notion that the involvement of the GM plays a major role in determining MS-related cognitive impairment.

Hippocampus. The hippocampus, including CA1, CA2, CA3 and CA4 subfields, with the dentate gyrus, and the subiculum are included in the hippocampal formation, which is located in the medial temporal lobe and connected with neocortical structures. These areas control several functions including memory formation, maintenance and retrieval, emotional memory processing (via amygdala, orbitofrontal, medial prefrontal cortex), and visuospatial memory and navigation (via precuneus and posterior cingulate cortex) (DeLuca et al., 2015). The first systematic evaluation of hippocampal demyelination was conducted by Geurts aand colleagues (2007), in which a total of 37 lesions were found in or around the hippocampus in 78.9% of the examined MS cases. Similar findings were documented in two other studies with a prevalence of 55-62% and about 30% of the afflicted hippocampal area. While subpial and subependymal demyelination is quite common, no hippocampal subregions appear to be spared (Dutta, et al., 2006; Papadopoulos et al., 2009). Recently, research has investigated the role of hippocampal atrophy in cognitive impairment. In their work, Sicotte et al. (2008) examined the absolute volume of both hippocampi and their segments in early RRMS, SPMS and healthy controls compared with performance on memory tasks. Both MS

groups had lower total hippocampal volume when compared with healthy individuals, which was localized in the CA1 regions in RRMS and more extensively in SPMS. Furthermore, memory performance was negatively correlated with total hippocampal, CA1 and subiculum volumes. Another study by Koenig and coworkers (2014) reported a 6-7% hippocampal volume reduction in people with MS compared to healthy subjects and a smaller hippocampal volume in MS patients who were compromised on memory and processing speed measures. Although relationships between hippocampal pathology and cognitive dysfunction are already starting to emerge, the mechanism by which this occurs is not fully understood.

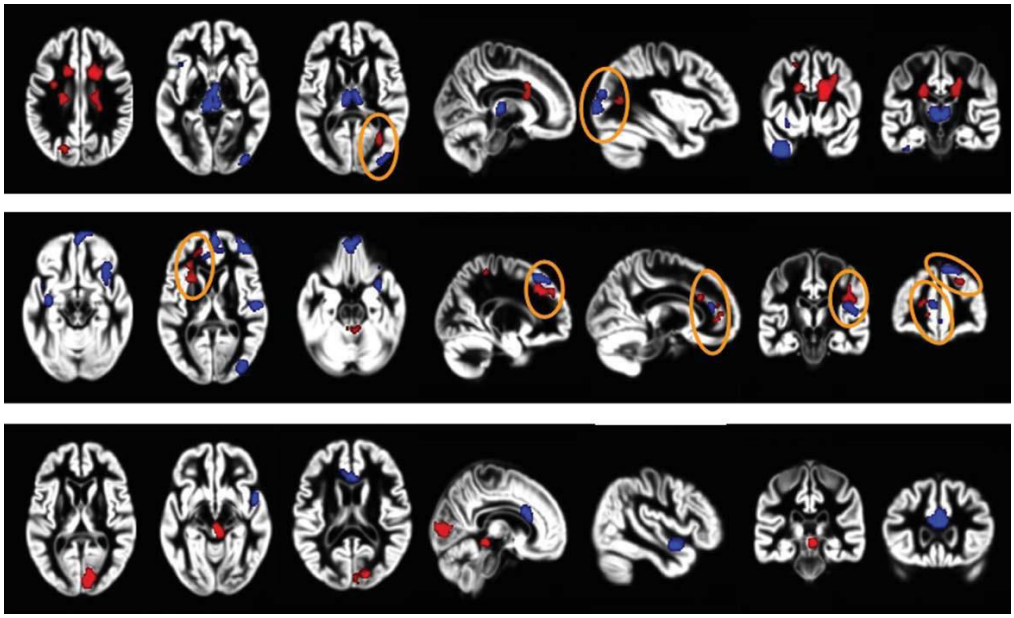

Figure 7. *T2 lesions, GM atrophy, and cognitive impairment in MS*. Distribution of regions of significant GM atrophy (blue) and T2-visible lesions (red) in cognitively impaired vs cognitively preserved patients with MS according to the clinical phenotype. Top row: RRMS; middle row: SPMS; bottom row: PPMS. Orange circles identify regions with a correspondence between presence of T2-visible lesions and GM atrophy. From Riccitelli et al. (2011). *Hum Brain Mapp*, **32**(10):1535-43.

2.4.1.3 Deep gray matter

Radiological studies have provided unequivocal evidence that atrophy in deep GM structures is prominent and contributes to cognitive dysfunction in MS. Deep GM consists of the thalamus, nucleus accumbens and basal ganglia, which encompass the caudate, putamen, globus pallidus, and amygdala. The mechanisms influencing deep GM tissue loss appear the same as those of the whole GM (DeLuca et al., 2015).

Thalamus. As a highly integrated structure, thalamus is an important gateway with multiple and reciprocal connections to cerebral cortical and subcortical structures critical for cognitive functioning, including hippocampus, amygdala, cingulate cortex, orbitofrontal cortex, retrosplenial cortex, and inferior parietal lobule. These different thalamic connections play a central role in arousal, executive functions, emotional and episodic memory, spatial learning and memory (Child & Benarroch, 2013; Minagar et al., 2013). Therefore, damage to thalamic structures or their connections can potentially have a notable impact on cognitive functions. It is also a main feature of both early and late MS (Henry et al., 2009; Houtchens et al., 2007). Measuring deep GM nuclei atrophy can provide important prognostic information, as suggested by the observation of patients with CIS, whose decreased thalamic volume over a 2-year period was associated with development of MS, or in relapse-onset patients, whose baseline thalamic atrophy was associated with the accumulation of disability after an 8-year follow-up (Rocca et al., 2010; Zivadinov et al., 2013). Classically, third ventricular width (TVW) has been used as a measure of whole brain atrophy, as larger ventricles indicate a larger amount of CSF and less brain tissue. Alternatively, TVW could represent a selective atrophy of the thalami, which border the third ventricle. Many works have found that TVW is a strong predictor of memory and processing speed impairments and is able to distinguish SP from RR courses of MS. When examining thalamus volume directly, researchers found that it is lower in MS patients compared to healthy controls and is associated with processing speed, working memory, verbal fluency, executive functions, verbal and visuospatial memory deficits (Batista et al., 2012; Benedict et al., 2004, 2006b; Houtchens et al., 2007). Post-mortem investigations have provided meaningful information on MS thalamic pathology, with neuronal loss and axonal damage as key elements of thalamic volume changes and with significantly more inflammatory lesions in WM than in GM (Cifelli et al., 2002; Haider et al., 2014; Vercellino et al., 2009). In particular, Cifelli and

colleagues (2002) observed an increased TVW (105%) and decreased total (21%) and medial dorsal (21%) nuclear thalamic volumes, with a similar reduction in neuronal density (22%). Vercellino and coworkers (2009) reported that predominant lesions, affecting both GM and WM structures, were found in periventricular areas of the thalamus involving cognitively relevant anterior and medial nuclei. Other studies examining deep GM nuclei showed a reduced volume in caudate, putamen, globus pallidus, nucleus accumbens, and thalamus, with the latter having an effect nearly twice that of any other structure. As for cognitive test correlations, thalamus was still strongly associated with measures of processing speed and executive functions, while nucleus caudate with working memory and verbal memory (Batista et al., 2012; Schoonheim et al., 2012). In short, research on thalamus pathological correlates of cognitive impairment has so far been limited, due to the complex anatomical architecture and lack of systematic studies on cognitively relevant thalamic nuclei. Despite these gaps, the demyelinating, inflammatory and neurodegenerative processes of the anterior and medial dorsal nuclei of the thalamus are established. Further connections with limbic and prefrontal cortical structures support the notion of the contribution of these nuclei to impaired processing speed, memory and executive functions.

Basal ganglia. The basal ganglia consist of the striatum, including caudate and putamen, and the globus pallidus. They receive inputs from thalamus intralaminar nuclei and several cortical regions, including frontal, inferotemporal and posterior parietal cortex, and participate in motor, oculomotor, cognitive and limbic circuits. There are numerous cortico-basal ganglionic loops, subsets of which connect the basal ganglia with dorsolateral prefrontal cortex, lateral orbitofrontal cortex and anterior cingulate/medial orbitofrontal cortices. All these frontal cortical regions are involved in executive functions (e.g., planning and attention) and rule-based learning and working memory – all cognitive domains affected in MS (Benarroch, 2012; Middleton & Strick, 2000). Despite the anatomical relevance of the basal ganglia to cognitive functioning, studies examining MS-related pathology in this region are relatively few (Haider et al., 2014; Vercellino et al., 2009). Basal ganglionic structures are affected by demyelination, but the extent to which they are damaged varies considerably, with the caudate nucleus more involved than putamen and globus pallidus. Most of these lesions are mixed involving both GM and WM, with a greater proportion of the lesions in the caudate appearing active

compared with putamen and globus pallidus. The extent of deep GM demyelination shows an intermediate amount of inflammation with respect to cerebral cortex and WM, which decreases significantly with age advancement and appears to contribute to clinical deficits, in addition to cerebral cortical and WM lesion burden (Haider et al., 2014; Vercellino et al., 2009). Neuronal loss and atrophy are features of basal ganglionic pathology in MS, but results are discordant. While a study by Haider and colleagues (2014) found no significant change between lesional and non-lesional deep GM, Vercellino and others (2009) observed a 35.5% reduction in neuronal density in demyelinated vs. non-demyelinated caudate nucleus, which was significantly associated with EDSS scores, but the impact on cognitive outcomes remained unexplored in the previous study (Haider et al., 2014). The relevance of basal ganglia on MS cognitive dysfunction is evidenced by strong correlations between MRI T2 hypointensity in caudate, globus pallidus, and putamen and cognitive measures (Brass et al., 2006). Similarly, the bicaudate ratio, i.e. the ratio of the width of the ventricles between the two caudate to the overall brain width, was found to be significantly greater in MS patients than healthy controls, in addition to being a strong predictor of processing speed impairment (Bermel et al., 2002). Finally, a significant relationship was observed between verbal fluency, verbal learning and memory deficits and lower volume in both caudate nuclei (Batista et al., 2012). Taken together, these works demonstrate that basal ganglia pathology is a core feature of MS. Given the intricate involvement of these deep GM nuclei in cortico-basal ganglionic loops with cortical regions implicated in memory and executive functions, these structures are likely to contribute to cognitive decline in MS.

2.4.2 The reserve concept

Originally developed in the field of normal aging and dementia, the concept of reserve was then applied to many neurological conditions, in an attempt to explain the discrepancy between brain damage and clinical manifestations in neurodegenerative diseases. The reserve is defined as “the hypothesized capacity of the mature adult brain to sustain the effects of disease or injury without clinical symptoms, but sufficient to

cause them in an individual possessing less cognitive reserve" (Starr & Lonie, 2007). This ability of the brain to tolerate pathology related to an underlying disease process without exhibiting overt signs or symptoms, allows those with greater baseline cognitive ability to adapt or compensate for changes caused by either normal aging or underlying disease damage. Therefore, individuals with better cognitive reserve would require more extensive pathology to cause the same degree of compromise than those with less reserve (Katzman et al., 1988; Whalley et al., 2004).

Recently, the reserve concept has been applied to the MS model, to explain the observation that not all people suffering from this condition present cognitive impairment despite having GM and WM pathology. This still-evolving theory refers to the capacity to retain cognitive abilities despite cerebral pathology, either as a result of greater baseline neuronal resources, higher neuronal efficiency, or more neural plasticity. There are two related conceptualizations of reserve within the context of genetics and premorbid behavior, the brain reserve and cognitive reserve, respectively (Stern, 2009). The first posits that reserve is a function of brain size or neuronal count. Brain reserve is considered a fixed construct of brain capacity, largely genetically determined, and is typically measured as a physical variable/proxy (i.e., head size, intracranial volume, synapse count). On the other hand, the concept of cognitive reserve involves the brain relying upon premorbid cognitive processes or compensation to combat brain damage. Cognitive reserve cannot be measured directly, and is typically evaluated using proxy variables associated with lifetime experience and/or intellectual enrichment (i.e., education, occupational attainment, intelligence, participation in cognitively stimulating activities). Of note, though there is no objective, physical substrate that fully explains cognitive reserve, this concept presumably relies on some neural processes. Early epidemiological research in older adults has described that the risk for developing dementia over time is substantially higher for those with low levels of education and occupational attainment, i.e. with low cognitive reserve (Stern, 2002, 2009).

Brain reserve

Originally proposed by Satz (1993) and subsequently conceptualized by Stern (2002), the concept of brain reserve assumes that clinical and functional deficits result once cerebral atrophy exceeds a certain critical threshold. This model also hypothesizes that there are

individual differences in this critical point, such that at a given level of disease pathology, some individuals demonstrate cognitive impairment, while others do not. In other words, subjects with larger brain reserve presumably have more neurons to lose before cognitive impairment manifests itself (Stern, 2002, 2009).

To date, only a few studies have examined the effects of brain reserve on cognitive functioning in people with MS. In all contributions, brain reserve was quantified based on intracranial volume, which is an accurate measure of head size and a proxy of maximal lifetime brain growth (MLBG) (Sandroff, Schwartz & DeLuca, 2016). Larger MLBG provides a low risk of cognitive decline because it is linearly related to larger neuronal count and, by extension, to synaptic count, which may support the development of robust neural networks resistant to disease-related disruption or provide additional degrees of freedom for plastic reorganization in response to the disease. In a series of studies, Sumowski and colleagues (2013, 2014, 2016a) tested the hypothesis of brain reserve in MS. A first cross-sectional work examined the effects of intracranial volume on markers of disease burden/cerebral atrophy (i.e., T2 lesion load and normalized GM/WM volumes) and cognition (processing speed, learning and memory) in 62 MS patients (Sumowski et al., 2013). Smaller intracranial volume and higher T2 lesion load were associated with slower processing speed. Importantly, intracranial volume explained the association between T2 lesion load and processing speed, so that larger MLBG reduced the negative impact of disease burden on speed of cognitive processing. Following the publication of the above paper, a few longitudinal investigations were then carried out. Sumowski et al. (2014), using the same MRI and cognitive parameters, examined whether greater brain reserve protected against cognitive decline in 40 MS patients over a 4.5-year period. Results on follow-up showed significant worsening of disease burden (i.e., increased lesion volume and reduced brain volume) and cognitive decline in their cohort. Lower MLBG was correlated with processing speed; and patients with low cognitive reserve evidenced greater decline in both processing speed and memory. After controlling for disease burden, subjects with larger MLBG showed lower decline in cognitive processing speed over 4.5 years. Recently, the same research group investigated whether larger MLBG was linked to lower risk for physical disability progression (EDSS score) over 5 years in a sample of treatment-naive Serbian patients with MS, independently of disease-related brain changes (T2 lesion volume, cerebral atrophy) (Sumowski et al.,

2016a). Larger MLBG predicted lower risk for disability progression, regardless of disease burden, and patients with smaller MLBG exhibited worse EDSS variation than those with larger MLBG. This study is the first extension of the brain reserve hypothesis to physical disability, showing that MLBG represents a stable, clinically available marker that can help assess risk for future disability in MS people. Another longitudinal study tested the brain reserve hypothesis by comparing the potentially moderating effects of MLBG on subcortical GM atrophy and processing speed, learning and memory in 71 subjects with MS and 23 matched controls over a 3-year period (Modica et al., 2016). Overall, cognitive performance and subcortical GM volume were reduced in patients compared to controls. Within the MS sample, subcortical GM volume, but not cognitive performance, significantly decreased over the 3-year period. Accordingly, MLBG did not explain differences in changes in cognitive functioning between MS and healthy subjects. These findings are inconsistent with those of Sumowski et al. (2014), and seemingly do not support the brain reserve hypothesis in MS. The authors have recognized that the conflicting results are not likely attributable to the measurement of intracranial volume, given the similarity in methodology between studies.

Research on the potential neuroprotective effects of brain reserve in people with MS is clearly in its infancy and further work is needed to better clarify the role of MLGB on cognition. An intrinsic limitation of this approach is that brain reserve is largely determined by genetics and is a fixed construct, making it difficult to consider the proxy of intracranial volume as an ideal target for intervention. Nevertheless, the research avenues that evaluate different proxies of cognitive reserve, largely reflecting behavioral processes, highlight potentially promising intervention approaches.

Cognitive reserve

Unlike the brain reserve hypothesis, there is a large body of literature on cognitive reserve in MS. Stern's theory (2002, 2009) states that individuals who process cognitive demands more efficiently can endure greater neural damage before cognitive impairment occurs. This cognitive efficiency could involve the use of alternative strategies (i.e., recruitment of differential brain networks or compensation) to maximize cognitive performance. Used proxies measure premorbid experiences and intellectual enrichment, which typically do not reflect ongoing behavior, and include demographic correlates (i.e., age, sex,

education), verbal intelligence, and participation in cognitive leisure, and others (i.e., occupational attainment). Some studies have also created multifactorial indices of cognitive reserve by combining these proxies into a single comprehensive measure. As proposed by Stern (2002, 2009), a key aspect of cognitive reserve concerns its ability to mediate the association between brain damage and the presence or absence of some clinical outcomes, i.e. cognitive impairment.

Several studies have investigated the protective effects of education alone on cognition and MRI outcomes in MS, which is considered an advantageous proxy of cognitive reserve. A preliminary study examined the effects of educational status on neuropsychological performance and global MRI measures of brain atrophy (i.e., brain parenchymal fraction/ventricular fraction) and lesion load volume in 43 MS patients and 43 matched controls (Bonnet et al., 2006). The low education MS group performed worse on almost all tests, while higher educated MS patients differed from controls only on measures of processing speed and attention. However, there were no differences in MRI-based measurements of brain atrophy or lesion load between the low- and high-education MS groups. Cognitive performance was more strongly correlated with MRI measures in the high-education MS group, suggesting that such patients demonstrated better cognitive performance than those with lower education, despite having a similar degree of brain atrophy/lesion load. Another cross-sectional study investigated the effects of years of education on multiple cognitive domains, and both local (i.e., TVW) and global (i.e., lesion load, normalized brain volume) MRI-based measures of disease burden in 137 MS patients (Pinter et al., 2014). An important result was the interaction between years of schooling and MRI outcomes (TVW and lesion load) on overall cognitive performance. The education by lesion load volume interaction was also significant on processing speed alone. This suggests that higher education can reduce the negative effects of both global (i.e., lesion load volume) and local (i.e., TVW) brain damage on cognition in MS patients. Martins Da Silva and colleagues (2015) also explored education as an indicator of cognitive reserve, while controlling for demographic, clinical and genetic (HLA-DRB1 and apolipoprotein E [ApoE]) features, in a sample of 419 MS subjects and 159 healthy controls. Patients with higher education were less likely to have cognitive deficits than those with lower education. Other significant predictors of cognitive impairment were age, EDSS, disease severity, and a progressive course. No significant association was

found with the HLA-DRB1 or ApoE ε4 alleles. The recent longitudinal study by Modica et al. (2016), described in the earlier section, extended these previous results by examining the effects of years of education on cognition and subcortical GM volume over a 3-year period. Unlike brain reserve, years of schooling explained differences in cognitive performance between MS patients and matched controls. In particular, processing speed decreased only in the cohort with the lowest education, and brain atrophy was associated with processing speed impairment in this group only. These findings suggest that greater cognitive reserve protects MS patients from cognitive decline associated with subcortical GM volume loss. Although education appears to exert protective effects on cognition associated with markers of brain atrophy/disease burden in MS, it might not sufficiently capture the complex construct of cognitive reserve. One issue with including education as a sole proxy concerns cultural differences, such as the requirements of compulsory education varying across cultures and countries. Therefore, other proxies have been included in cognitive reserve research in MS.

A number of studies have examined premorbid verbal intelligence (i.e., vocabulary) alone as a proxy of cognitive reserve in people with MS, given that it is generally resistant to age-related decline and independent of neurological damage. Sumowski and colleagues (2009) investigated whether the negative impact of brain atrophy on information processing speed and efficiency was moderated by cognitive reserve. Using SDMT and PASAT as processing speed measures and TVW as atrophy index, their findings highlighted that the adverse effects of brain atrophy on processing speed were moderated by estimated pre-morbid intelligence. This study also showed a significant interaction between atrophy and cognitive reserve, meaning that among patients with severe brain atrophy, those with greater cognitive reserve had better neuropsychological performance, but the same was not the case for patients with minimal atrophy. Similarly, another cross-sectional study by the same group (Sumowski et al., 2010a) extended these results to include learning and memory. Even in this case, the effects of significant atrophy on verbal learning and memory were reduced as a function of increasing verbal intelligence. Sumowski et al. (2010b) also investigated a potential neural mechanism of the protective effects of verbal intelligence on cognitive processing speed in 18 MS patients. Measures included verbal intelligence (vocabulary task), processing speed (SDMT), and brain atrophy (TVW), and participants also performed an N-back fMRI task to examine

patterns of cerebral activation as a potential neural basis of cognitive reserve. Consistent with the aforementioned pattern of results, increased verbal intelligence reduced the negative effects of brain atrophy on processing speed. Of note, higher verbal intelligence was associated with lower activation of the prefrontal cortex and greater activation of the anterior cingulate cortex (i.e., default-mode network) in both lower and higher cognitive demands during the N-back activity, in addition to a better task performance in the latter condition. Overall, verbal intelligence appears to be a strong measure of cognitive reserve in people with MS, but it cannot yet be considered a gold-standard reserve proxy. In addition to there being no longitudinal studies on higher verbal intelligence alone, this measure of lifetime experience also reflects crystallized ability, and therefore could be a difficult target for intervention. To that end, other measures of cognitive reserve might represent better targets for rehabilitation to reduce the effects of MS-related brain atrophy on cognition.

Premorbid cognitive leisure activity has been operationalized as a proxy of cognitive reserve and provides a generalizable measure of lifetime experience, as it is not influenced by disease state. Another advantage is that participation in cognitively stimulating activities could be targets for intervention, as they are more susceptible to change than other proxies. These leisure activities include reading for pleasure, producing art, non-artistic writing, playing a musical instrument, playing games/cards, and participating in hobbies (Sandroff, Schwartz & DeLuca, 2016). Consistent with MS research on education and verbal intelligence, participation in more premorbid cognitive leisure demonstrated a decrease in the negative impact of brain atrophy on processing speed, verbal learning and memory. More interestingly, these effects were over-and-above those of the education years and verbal intelligence (Sumowski et al., 2010c). A more recent study, described in the previous section, by the same group extended these results by comparing the effects of brain reserve (i.e., intracranial volume) with those of premorbid cognitive leisure on processing speed, learning and memory, and disease burden (i.e., T2 lesion load) in 62 MS patients (Sumowski et al., 2013). Results showed that cognitive reserve (i.e., premorbid cognitive leisure) moderated the effects of T2 lesion load on overall cognitive performance and, similarly, on memory, but not on processing speed. All these effects were significant over-and-above those of brain reserve to the point that premorbid cognitive leisure seemed to have protective effects on MLBG-

independent cognition. Since the influence of premorbid cognitive leisure was greater in memory processes, the same research group recently examined the effects of this proxy on verbal and visual memory, hippocampal volume, and global brain atrophy in 187 RRMS patients (Sumowski et al., 2016b). Intellectual enrichment was specifically related to the larger hippocampal volume. Premorbid cognitive leisure moderated the negative relationship between global brain atrophy and normalized hippocampal volume, whereby patients with more early enriching life experiences maintained hippocampal volume better when faced with global brain atrophy. Moreover, hippocampal volume partially mediated the relationship between premorbid cognitive leisure and verbal learning and memory, providing a key component of the neuroanatomical basis of reserve against memory decline in MS. Again, a good amount of evidence supports the protective effects of premorbid leisure on cognitive processes, but there is an overall lack of longitudinal studies.

Since there is no 'gold-standard' proxy of cognitive reserve, several studies have considered a combination of factors related to lifetime experience/intellectual enrichment for operationalizing cognitive reserve in MS, seeking to overcome the limitations of single proxies. In a preliminary 5-year longitudinal study (Benedict et al., 2010), it was found that cognitive reserve, with education and verbal intelligence as indicators, predicted decline in cognitive processing speed, based on a composite index of SDMT and PASAT scores, over the 5-year period. However, patients with high education (at least 15 years) did not show significant changes on SDMT, while those with less education (i.e., less than 15 years) demonstrated a significant impairment over time. Some researches have simultaneously examined multiple proxies of cognitive reserve that included other factors. For instance, one study investigated the effects of occupational attainment, years of education, and verbal intelligence separately on cognitive functioning and brain atrophy in 72 MS individuals (Ghaffar, Fiati & Feinstein, 2012). Occupational attainment accounted for significant variance in measures of processing speed, learning and memory, and executive functioning over-and-above brain atrophy and verbal intelligence, while education was not predictive of any cognitive outcome. These findings suggest that occupational attainment reduces the negative effects of brain atrophy on multiple cognitive domains in MS, regardless of verbal intelligence and schooling, but they are also inconsistent with the effects of education found in previous

research. Another study, using a longitudinal design, examined the influence of cognitive reserve, using a composite proxy (years of education, verbal intelligence and premorbid cognitive leisure activity), on cognitive decline and brain atrophy over a 1.6-year period in 52 RRMS patients (Amato et al., 2013b). At baseline, cognitive reserve predicted performance on measures of processing speed, learning, memory, and verbal fluency over-and-above brain atrophy measurements. However, cognitive reserve did not predict cognitive decline as opposed to progressing brain atrophy at follow-up, probably due to the lack of substantial cognitive decline over a short time period.

Although brain reserve and cognitive reserve appear to provide protective effects in people with MS, the results of studies examining multiple proxies are heterogeneous and a single proxy may not be sufficient to embrace the complex construct of cognitive reserve. Perhaps more importantly, there is exciting evidence that reserve cannot be limited to premorbid factors (i.e., genetics and early-life behavior) that are not highly susceptible to change. Rather, reserve can be built based on the additive and cumulative effects of present activities. The concept of reserve-building involves the current participation of individuals engaged in cognitively stimulating activities even after MS diagnosis, which could protect against cognitive decline (Schwartz et al., 2015; Sumowski, 2015). Indeed, there is burgeoning evidence that ongoing participation in intellectually enriching activities (e.g., current hobbies, cultural, and leisure activities) could protect against worsening of MS disability (i.e., symptoms, ambulatory status). In a series of studies, Schwartz and colleagues (2013a, 2013b) measured the effects of previous and current participation in cognitively stimulating activities on disease-related disability in large samples of people with MS. In the first work on 1142 participants, the results showed that patients who took part in more cognitively stimulating activities, both previously and currently, reported lower MS disability. Current participation was independently associated with patient-reported better physical and psychological function and well-being, while previous participation was independently correlated only with well-being (Schwartz et al., 2013a). These authors then completed a longitudinal study involving 859 MS patients over a 5-year period (Schwartz et al., 2013b). At follow-up, current, but not previous, participation in cognitively stimulating activities was associated with less worsening of disability over time. The authors have suggested that perhaps ongoing participation in intellectually enriching activities builds reserve and provides a

buffer against worsening of MS-related disability beyond the influence of previous participation in such activities (i.e., baseline reserve). Emerging evidence supporting the concept of reserve-building is promising, as it highlights ongoing participation in cognitively stimulating activities as a target for potential rehabilitation interventions that may be able to increase reserve and potentially protect against physical and psychological MS-related decline. These beneficial effects appear to be independent of previous/premorbid attendance in intellectually enriching activities. However, it is unknown if current participation in such activities protects against the expression of disability at certain levels of brain damage in MS. In addition, previous research has included patient-reported measures (i.e., ambulatory disability, symptoms, psychological well-being), but not neuropsychological tests.

There is a growing body of evidence supporting the concept of reserve for reducing the effects of disease burden on cognitive functioning in individuals with MS. Overall, across a variety of individual and multifactorial proxies, greater MLBG, and lifetime experience/intellectual enrichment seemingly protect against disease-related cognitive impairment and decline. Despite the fact that there are different effects and limits of brain reserve and cognitive reserve on cognitive functioning in MS, depending on the proxies that are adopted, this is entirely consistent with Stern's (2002, 2003) conceptualization of reserve as a complex and multifactorial construct. Research on reserve provides an important framework for the development and application of rehabilitation approaches to ultimately mitigate the impact of neural damage related to the disease. Such intervention approaches will presumably involve changing targets for reserve-building, that is, participating in cognitively stimulating activities, to potentially improve cognitive dysfunction in people with MS.

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CHAPTER III

Functional and Morphological Correlates of Cognitive and Social Cognition Impairment in Multiple Sclerosis: A Longitudinal Study

3.1 Scope of the thesis

The main purpose of the present study was to examine the effect of MS on cognition and brain structure, by combining neuropsychological and morphological investigations.

Firstly, to identify any indicator and/or pattern of cognitive impairment, we investigated several cognitive domains and performed atrophy measurements in RRMS diagnosed outpatients with short disease duration and minimal physical disability, and compared them with healthy subjects. In particular, we focused on executive and memory functions and their relationship with clinical and neurological variables. We also correlated volumetric parameters with neuropsychological measures in order to identify the brain structures for which reduced integrity was able to better predict cognitive performance.

Secondly, we were interested in analyzing the main MS-related cognitive changes over time. Therefore, we re-tested the group of RRMS patients after six months with an abridged cognitive battery and then repeated the same neuropsychological and morphological analyses after one year, comparing them with healthy counterparts.

Finally, to verify the impact of MS on social skills and psychological well-being of patients, we explored many aspects of social cognition, mood, fatigue, psychological symptoms, and quality of life at both the beginning and the end of the study.

3.2 Materials and methods

3.2.1 Participants

The current study was conducted in accordance with the Declaration of Helsinki and after obtaining the St. Gerardo Hospital Ethics Committee protocol approval. All participants signed an informed consent after an adequate presentation of the goals and investigations envisaged by the study, and each of them was provided with an identification code to keep confidentiality.

3.2.1.1 MS Patients

Forty-two consecutive RRMS patients were recruited from the Neuroimmunology Center of St. Gerardo Hospital in Monza (MB), Italy.

Inclusion criteria were a clinically defined MS diagnosis (Polman et al., 2005), age between 18 and 50 years, and an EDSS score ≤ 4. Exclusion criteria included a history of psychiatric or neurological disorders other than MS, current or past substance abuse, any motor or visual impairment that could interfere with cognitive assessment, inadequate reading or writing skills, clinical relapses or corticosteroid treatment within the previous 4 weeks.

All patients underwent a neurological examination to estimate the disability level and all of them were under treatment with disease-modifying drugs, including beta-interferon (n.20, 47.8%), glatiramer acetate (n.15, 35.7%), dimethylfumarate (n.4, 9.5%), and teriflunomide (n.3, 7.1%).

MRI investigation was performed within the already planned clinical routine. Due to instrument artefacts, imaging data were acquired from 38 out of 42 patients at baseline and from 30 patients at one-year follow-up.

3.2.1.2 Healthy controls

The participants who took part in this work as healthy controls (HC) were never previously enrolled for similar studies. They were divided into two groups for cognitive evaluation and for MRI acquisition, respectively. Both measurements were detected only once at the baseline.

For the neuropsychological assessment, 30 volunteers were recruited from the local community to minimize the possibility that they were familiar with cognitive testing, and they were matched to RRMS patients for age, gender and educational level.

As far as structural imaging, 17 age-matched healthy subjects were selected among the St. Gerardo Hospital personnel.

All controls had no history of neurological or psychiatric illness or of drug or alcohol abuse.

3.2.2 Data collection protocol

A detailed evaluation of cognitive, social, emotional, and behavioral functioning was performed on all participants in two sessions of one hour each to minimize tiredness and loss of concentration. Questionnaires for fatigue and quality of life were only administered to the patient group. For details on the subject case report form (CRF), see Appendix.

3.2.2.1 General neuropsychological assessment

Each subject underwent the following standard neuropsychological battery and testing set to evaluate specific cognitive abilities.

Global cognitive evaluation

Brief Repeatable Battery of Neuropsychological Tests (BRB-NT; Rao, 1990; Amato, 2006):

- Selective Reminding Test (SRT-LTS, SRT-CLTR, SRT-D) – verbal learning and long-term memory.

This test measures verbal learning and memory during a list learning task of six trials. The list consists of 12 words that the examiner reads and the subject is instructed to recall them all. For each consecutive trial, only the words that are missed on the preceding trial are given. After 15 minutes, following the PASAT administration, the subject is asked to recall the word list. The SRT distinguishes between short- and long-term components of memory and examines also the consistency of retrieval from long-term memory. Three SRT indices have been used in our study: words repeated twice and above are considered to have entered in long-term storage (LTS); if a word in LTS is consistently recalled in all subsequent trials it is scored as in Consistent Long Term Retrieval (CLTR); the total number of words recalled after the delayed period (SRT-D).

- 10/36 Spatial Recall Test (SPART, SPART-D) – visuospatial learning and long-term memory.

This task consists of a 6x6 checkerboard with ten tokens randomly placed. The board is put in front of the subject for ten seconds. After presentation, the subjects attempt to reproduce the original design on an empty board. This process is repeated three times and after 15 minutes, following the SRT-D, in which the subject is asked to recall the design again. The score is the total number of correct responses for the three trials (SPART) and the delayed recall trial (SPART-D).

- Symbol Digit Modalities Test (SDMT) – visual information processing speed, sustained attention and working memory.

SDMT assesses sustained attention and concentration by primarily evaluating complex visual scanning and tracking. The subject examines a series of nine meaningless geometric symbols which are labelled 1 to 9. Within a duration of 90 seconds, the subject substitutes symbols in a row by the corresponding number and responds verbally. The score is the number of correct substitutions.

- Paced Auditory Serial Addition Test (3-second and 2-second PASAT) – auditory information processing speed, sustained attention and working memory.

PASAT is a measure of sustained attention and information processing speed by adding pairs of digits presented at two rates of speed. The subject is instructed to add 60 pairs of digits such that each number is added to the one that immediately precedes it and to report the outcome verbally. The digits are presented by tape, first with a speed of every 3 seconds one digit and the second trial with every 2 seconds. The subject is required to respond verbally quickly, inhibit encoding of his/her own response while attending to the next stimulus in a series, and perform at an externally determined pace. The score is the number of correct responses per trial (PASAT-3, PASAT-2).

Memory

- Digit span forward and backward (Monaco et al., 2013) – verbal short-term span and working memory.

A sequence of numbers is read by the examiner and the subject recalls the numbers in the same or reverse order. The number of repeated digits in the forward condition is a measure of auditory memory span, while the backward condition involves the ability of attention and encoding, phonological working memory, cognitive control and manipulation.

- Corsi block-tapping test (Monaco et al., 2013) – visuospatial short-term and working memory.

The traditional version consists of nine square blocks positioned on a wooden board. The examiner taps the blocks starting with sequences of two cubes. The subject has to reproduce a given sequence by tapping the blocks in the same (forward), or reverse (backward) order. These steps are repeated several times with different lengths by increasing one block at time, until the number of wrong reproductions is three out of five. The number of correct reproductions in the forward condition is a measure of the visuospatial memory span, while the backward condition is an indicator of the visuospatial working memory ability.

- Brief Story Test (Novelli et al., 1986a) – verbal short- and long-term memory.

A brief chronicle text is read aloud by the examiner and the subject is asked to remember the details trying to use the same words, both immediately and 10 minutes after the second reading of the tale. The task is a reliable measure of immediate or delayed story recall test. A global score is obtained by averaging the two recall scores.

- Rey-Osterrieth Complex Figure (ROCF; Caffarra et al., 2002) – visuoconstructive ability, strategy planning, complex visual perception and organization, and visuospatial long-term memory.

The task consists of two conditions. First, subjects are given the ROCF stimulus card, and then asked to draw the same figure. After a delay of 15 minutes, they are instructed to draw what they remembered. The two scores obtained by the copy and recall conditions are a measure of visuoconstructive and planning skills, and visuospatial long-term memory, respectively.

Verbal fluency

- Semantic fluency (Novelli et al., 1986b) – language and memory knowledges.

The task is a measure of lexical retrieval assessing the spontaneous production, in one minute, of words from three specific categories (fruit, animals, car brands). A global score is calculated by averaging the number of words recalled in the three trials.

Visual perception

- Street's Completion Test (Spinnler & Tognoni, 1987) – visual perception and discrimination abilities.

The test is based on the Gestalt concept of visual closure evaluating visual integration ability. It consists of two examples and 14 cards in which black blotches representing parts of objects have to be recognized; therefore, participants have to group the parts into a recognizable figure. The score is the number of correct answers.

Attention and executive functions

- Stroop Colour-Word Test (Barbarotto et al., 1998) – selective attention, information processing speed and interference inhibition.

Subjects are required to read three different tables as fast as possible in 30 seconds. Two of these represent the 'congruent condition' in which participants are asked to read names of colors (word reading condition) printed in black ink and to name different colored squares (color naming condition). In the third table, namely the inhibition condition, color-words are printed in an incongruent color ink. The participants are required to name the ink color while inhibiting the interference from reading the word. This difficulty in inhibiting the more automated process is called the 'Stroop effect' and the score is obtained by the number of correct answers in the third table.

- Phonemic fluency (Novelli et al., 1986b) – executive functioning, information processing speed and language skills.

The task assesses the spontaneous production in one minute of words that begin with three specific letters (F, P, L), and it is therefore a sensitive indicator of executive dysfunction. A global score is calculated by averaging the number of words recalled in the three trials.

- Wisconsin Card Sorting Test (WCST; Laiacona et al., 2000) – abstract reasoning, mental flexibility and problem-solving.

WCST is a non-speed executive task as well as a test of set-shifting, i.e. the ability to display flexibility in the face of scheduled reinforcement changes, in which the subject must determine and maintain a sorting strategy and adjust it according to the feedback. The test consists of 128 cards and there are three different criteria (color, shape, or number of the symbols) to classify each card. The only feedback is whether the criterion is correct or not and the classification rule changes every 10 cards. The task generates a number of psychometric scores, but the dependent measures used in this study have included the global score, failure to maintain set, perseverative and non-perseverative errors.

- Frontal Assessment Battery (FAB; Appollonio et al., 2005) – screening of global executive functioning.

A brief tool for evaluating executive functions, it is composed of six subscales: similarities (conceptualization), lexical fluency (mental flexibility), motor series 'Luria' test (programming), conflicting instructions (sensitivity to interference), Go-No-Go (inhibitory control), and prehension behavior (environmental autonomy). A global score is obtained by the sum of these subtests.

3.2.2.2 Social cognition and ToM assessment

Cognitive and affective ToM

The *Faux Pas Recognition Test* (Stone, Baron-Cohen & Knight, 1998) is designed to assess the ability to infer mental states of characters involved in 20 stories, half of which portray inappropriate social behaviors based on false-beliefs. Each story is read aloud by the examiner as well as presented in written form on a cardboard. The subject has to detect the social *faux pas* and answer the following four questions: 1. '*faux pas* detection' question – the ability to identify if and which character said something hurtful or insulting to another person; 2. 'false-belief' question – the ability to make an inference as to why the protagonist could have a mistaken belief that was different from reality; 3. 'unintentional' question – the ability to recognize that the person committing a *faux pas* was unware of saying something inappropriate; 4. 'emotional' question – the ability to understand that the person hearing the *faux pas* might have felt hurt or insulted. Performance is scored only for correctly identifying the stories containing *faux pas*, assigning one point based on appropriateness of the answer to each question and thus obtaining a global score and four subscores. If the identification of the *faux pas* is incorrect, the subjects are asked for control questions to evaluate if their comprehension of the story is sufficient, but a score of zero is assigned.

Cognitive and affective ToM, and adherence to shared norms

Cognizione Sociale e Comportamento (Prior, Sartori & Marchi, 2003) is the Italian adaptation of the *Social Cognition and Behavior* battery originally developed by Blair and Cipolotti (2000). The abridged version consists of the following three tasks:

- *Theory of Mind Test*. This test allows to investigate the subject's ability to put him- or herself in someone else's shoes and understand others' mental states. It consists of 13 short stories describing social and family situations and the subject is asked to explain why the protagonists behaved the way they did in the stories. The score is assigned according to the ability of mentalizing shown by the subject.
- *Emotions Attribution Test*. This task consists of 58 short stories in which the subject is asked to describe what emotion the protagonist experienced. Seven emotions are illustrated: embarrassment, sadness, fear, anger, happiness, disgust, and envy. The performance is scored for each emotion correctly identified.
- *Social Situation Test*. This test measures the ability to distinguish social 'normative behaviors' from 'violations', i.e. actions that violate common social norms and generate negative reactions. The subject is presented with 25 social situations and asked to rate characters' behaviors from 'normal' to 'extremely strange' on a four-point scale. Three indices are calculated: the number of correctly identified normative behaviors and violations, and the degree attributed to violations by the subject.

3.2.2.3 Emotional and behavioral assessment

Mood

- Beck Depression Inventory (BDI; Beck et al., 1961) – affective, cognitive, motivational, vegetative, and psychomotor components of depression.

BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression including mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideation, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia,

fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. The total score is obtained by adding the scores of all the items.

- State-Trait Anxiety Inventory - X Form (STAI-X; Spielberger et al., 1983) – distinction between state anxiety, as a symptom, and trait anxiety, as usual response to external stimuli.

STAI-X is a 40-item, self-rated scale to measure the presence and severity of current symptoms of anxiety and a generalized tendency to be anxious. There are two subscales, each of which consists of 20 items. The former evaluates the current state of anxiety (STAI-X1), asking how respondents feel "right now", and includes subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The second scale assesses relatively stable aspects of "anxiety proneness" (STAI-X2), including general states of calmness, confidence, and security. The total score for each subscale is the sum of all the items.

Psychological symptoms

- Symptom Checklist-90 (SCL-90; Derogatis, Lipman & Covi, 1973) – presence and severity of symptoms of psychological distress.

SCL-90 is a 90-item, self-report questionnaire designed to evaluate a broad range of psychopathological problems and symptoms. The principal symptom dimensions that provide nine indices are labelled: Somatization (SOM), Obsessive-Compulsive (O-C), Interpersonal Sensitivity (INT), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), and Psychoticism (PSY). The global measure referred to as the Global Severity Index (GSI) is an indicator of the level of psychological distress and maladaptation.

Fatigue

- Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) – impact of fatigue and exhaustion on the physical, psychosocial and cognitive status.

MFIS is a structured, self-report questionnaire consisting of 21 items, and is based on items derived from interviews with MS patients concerning how fatigue impacts their lives. The total score is the sum of 21 items.

Quality of life

- Multiple Sclerosis Quality of Life-54 (MSQOL-54; Solari et al., 1999; Vickrey et al., 1995) – quality of life based on two main dimensions, physical health and mental health.

MSQOL-54 is a multidimensional health-related quality of life measure combining both generic and MS-specific aspects. This 54-item instrument generates 12 subscales along with two additional single-item measures (sexual function and change in health), and two summary scores (physical health and mental health). The subscales include physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perception, social function, cognitive function, health distress, overall quality of life, and sexual function.

3.2.2.4 Statistical analysis

All statistical analyses were carried out with SPSS 24.0 (IBM Corp, 1989-2016, Armonk, NY) software. At baseline, group differences between patients and healthy subjects on socio-demographic, clinical and neuropsychological characteristics were analyzed using Student's *t*-test or chi-square as appropriate; while non-parametric Mann-Whitney's *U* test was used for comparing social cognition scores and self-report questionnaires. For follow-up evaluations in RRMS group, only neuropsychological measurements were tested after six months, while after one year the assessment was overlapped with the baseline. Analysis of variance (ANOVA) with repeated measures or Wilcoxon signed-rank test with post-hoc tests and group comparison were performed to detect any cognitive changes occurring during the time period between the different evaluations in RRMS group and between patients and controls, respectively. The suggested *p* value

required for significance, after Bonferroni correction for multiple tests, was set at 0.002 for all analyses.

Identification of MS patients with general neuropsychological or social cognition deficits at the single case level was also carried out by calculating Z scores using controls' mean scores and standard deviations. A test was considered a failure if the standardized score was lower than the fifth percentile of the control distribution (≥ 2.0). The fifth percentile cut-off is a psychometric criterion commonly used in clinical practice to determine cognitive impairment (Lezak, Howieson & Loring, 2004). It is frequently employed in MS research to discover or highlight faulty ability in the face of an intact performance (Calabrese, 2009; Dulau et al., 2017; Pravatà et al., 2017). The percentage of low scores displayed by RRMS patients within and between different time-points was then calculated.

The discrepancies between total brain and GM/WM volumes in RRMS and healthy subjects were performed with Student *t*-test and only significant differences were further analyzed with linear regression models. Before examining the contribution of any variable to brain volumes in the RRMS group, individual cognitive tests were entered into a correlation matrix. Since these measures were closely associated with each other, especially those speed-based, we chose to compute five composite scores to reduce the number of correlations (Dulau et al., 2017; Genova et al., 2012; Planche et al., 2016), by averaging the Z scores on the tests that made up each measurement, thus obtaining the following main dimensions: Verbal Memory (all subscores of SRT, forward digit span and Brief Story task), Visuospatial Memory (all subscores of SPART, forward Corsi block and ROCF-delay recall), Non-speeded Executive Functions (backward digit span and Corsi block, and WCST global score), Speeded Executive Functions (SDMT, PASAT-3 and PASAT-2, Stroop task, and phonemic fluency), and Visual Skills (ROCF-copy and Street task). As a second step, stepwise regression analysis (entrance criterion $p \leq 0.05$ and exit criterion $p \geq 0.10$) was carried out to assess the relative contribution of the main cognitive (five dimensions), socio-demographic (age, sex, education level) and clinical (disease duration and EDSS) measures in predicting reduced brain volume in the RRMS group.

3.2.3 MRI protocol and analysis

RRMS patients and selected controls underwent a brain MRI using a 1.5T system (Achieva, Philips Healthcare) with maximum gradient strength of 33mT/m and slow rate of 80mT/m/ms. For patients, MRI protocol was conducted within their clinical routine with the acquisition of the following standard images: axial and coronal T2-weighted turbo spin-echo (TSE), axial T2-weighted FLAIR, and axial diffusion weighted imaging (DWI) sequences. Brain volume comparison was performed using the 3D T1-weighted gradient-echo (GRE) sequence (repetition time [TR] = 25 ms, echo time [TE] = 4.6 ms, flip angle = 30°, matrix size = 240 x 240 mm, field of view = 240 x 240 mm^2, 135 contiguous axial slices, slide thickness = 1 mm, voxel size = 1 x 1 x 1 mm).

Analyses were carried out with SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, Institute of Neurology, London) software. All brain volume images were processed with the VBM (Voxel Based Morphometry) tool, spatially normalized to the internal template and then segmented into GM, WM and CSF.

At the baseline and follow-up, group comparison was conducted using the two-sample Student's *t*-test, with sex and age as covariates. These investigations were aimed at two main goals: on the one hand, to detect significant morphological differences between patient and control GM volumes; on the other hand, to identify a statistically significant volumetric variation between the baseline and one-year MRI measurements in RRMS group. GM regions showing a significant reduction were also related to a stereotaxic atlas with specific anatomical areas. Only clusters corresponding to at least 100 contiguous voxels were selected and identified by the AAL (Automated Anatomical Labeling) tool, a package for the anatomical labeling of functional brain mapping (MICCAI 2012, Grand Challenge and Workshop on Multi-Atlas Labeling). In this tool, the intersection of each cluster and the Anatomical Volumes Of Interest (AVOI) was computed and the result was sorted in a descending order according to the percentage of overlap, reporting the coordinates in mm (x, y, z) of the most significant local maxima of the cluster and the list of anatomical labels and percentage of overlap. Percentage less than 1% was not listed

and, if part of the region was outside the parcellation, the anatomical label was listed as 'outside area'.

In RRMS group, Pearson's *r* coefficient was calculated for correlation analysis between GM/WM regions and cognitive measures, with age, sex, education level, EDSS, BDI and MFIS as covariates. For all analyses, level of significance was set at $p < 0.005$ in order to control for Type I error.

3.3 Results

3.3.1 Socio-demographic and clinical data

The final study sample comprised 42 RRMS patients and 47 healthy subjects, whose socio-demographic and clinical features for cognitive and MRI investigations are compared in Table 3A and 3B, respectively. As for cognitive testing, patients did not differ significantly from controls in terms of age, gender, and education years (**Table 3A**). Considering MRI sample (**Table 3B**), the RRMS and HC groups were statistically similar for age and sex, but not for level of education that was significantly higher in controls than in patients at both baseline and one-year follow up.

	RRMS (n. 42)	HC (n. 30)
Age	34.8 ± 9.3	33.9 ± 9.6
Education (years)	13.1 ± 3.4	13.5 ± 3.3
Sex (no of men/women)	15/27	12/18
Disease duration (months)	23.1 ± 16.3	–
EDSS mean (range 0-3.5)	1.6 ± 1.1	–
Treatment duration (months)	15.2 ± 14.6	–

Table 3A. Socio-demographic and clinical features of patients with relapsing-remitting multiple sclerosis and healthy controls for cognitive testing.

	RRMS		HC
	baseline (n. 38)	follow-up (n. 30)	(n. 17)
Age	34 ± 9.1	33.9 ± 9.4	35.3 ± 6.2
Education (years)	13.4 ± 3.6	13.3 ± 3.7	**16.1[a] ± 2.1**
Sex (no of men/women)	12/26	9/21	4/13
Disease duration (months)	22.8 ± 16.4	20.6 ± 15.9	–
EDSS mean (range 0-3.5)	1.5 ± 1.1	1.4 ± 1	–
Treatment duration (months)	15.6 ± 14.6	14.2 ± 14.2	–

Table 3B. Socio-demographic and clinical features of patients with relapsing-remitting multiple sclerosis at the baseline and one-year-follow-up, and healthy controls selected for structural neuroimaging; $p = 0.001$ versus [a]RRMS
Note. The two control groups, for cognitive and morphological investigations, were significantly different from each other only for the level of education ($p = 0.006$)

3.3.2 Baseline data

Neuropsychological test results

Comparison of mean scores obtained by patients and controls is reported in superscript in **Table 4A**.

At group level, RRMS patients were significantly impaired with respect to our healthy subjects on SPART and SPART-D, backward digit span and Corsi block, brief story recall, Street test, Stroop task, phonemic fluency, and 2-sec PASAT.

Considering Z scores, 26.2% (N. 11) of the RRMS group showed no impairment on any test, 21.4% (N. 9) was impaired for at least one test, 7.1% (N. 3) for at least two tests, and 45.3% (N. 19) in three or more tests. The proportions of patients with cognitive impairment for major cognitive domains (verbal and visuospatial memory, speed and not speed-based executive functions, and visual abilities) are shown in **Figure 8A**.

	RRMS (n. 42)	HC (n. 30)
Selective Reminding Test		
- Long Term Storage	51.9 ± 14.9	61.6 ± 12.5
- Consistent Long Term Retrieval	45.8 ± 18.7	57.6 ± 16.2
- Delay Recall	9.3 ± 2.4	10.7 ± 1.5
Spatial Recall Test		
- Immediate Recall	**20.4[a] ± 5.3**	25.2 ± 3.6
- Delay Recall	**7.4[a] ± 2.2**	8.9 ± 1.6
Digit span, forward	6.3 ± 1	6.8 ± 0.9
Digit span, backward	**4.6[a] ± 0.9**	5.8 ± 1.1
Corsi block, forward	5.7 ± 1.1	6.5 ± 1
Corsi block, backward	**5.1[a] ± 1**	6 ± 1.1
Brief story recall	**15.3[a] ± 3.5**	20.3 ± 3.9
Rey-Osterrieth Complex Figure		
- Copy	35.1 ± 1.2	35.4 ± 0.9
- Delay Recall	21.3 ± 5.2	24.1± 4.9
Street's Completion Test	**9.2[a] ± 1.9**	10.6 ± 1.5
Stroop Colour-Word Test	**30.6[a] ± 6.8**	38.1 ± 6
Phonemic fluency	**37.3[a] ± 7.6**	45.8 ± 9.3
Semantic fluency	47.4 ± 7.9	50.3± 7.7
Symbol Digit Modalities Test	57.1 ± 12.4	64.1 ± 12.6
Paced Auditory Serial Addition Test		
- 3 sec trial	45.6 ± 10	52.1 ± 7.5
- 2 sec trial	**34.5[a] ± 11.5**	43.4 ± 11.5
Frontal Assessment Battery	17.7 ± 0.6	17.8 ± 0.5
Wisconsin Card Sorting Test		
- Global score	15.5 ± 7	14.2 ± 6
- Perseverative errors	6.4 ± 2.3	5.3 ± 1.5
- Non-perseverative errors	4 ± 2.2	3.9 ± 1.8
- Failure to maintain set	0.3 ± 0.6	0.1 ± 0.3

Table 4A. Raw mean scores of cognitive tests obtained by patients with relapsing-remitting multiple sclerosis and healthy controls; $p \leq 0.002$ versus [a]HC

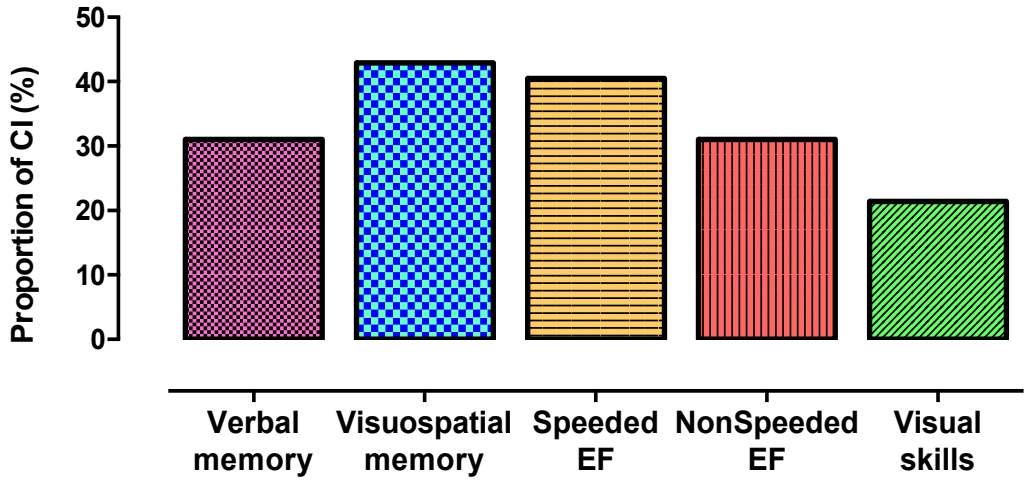

Figure 8A. Proportion of relapsing-remitting multiple sclerosis patients with impaired cognition; CI, cognitive impairment; EF, executive functions

Social cognition measure results

Group comparison showed no significant difference for the Faux Pas, Theory of Mind and Social Situation tasks. Regarding the Emotion Attribution Test, RRMS group was significantly impaired than controls on the recognition of sadness and anger, but not of other emotions (**Table 4B)**.

At the single-case level, 14.3% (N. 6) of RRMS patients showed no abnormal score on social cognition measures, 35.7% (N. 15) were compromised in one measure, 21.4% (N. 9) in two, and 28.6% (N. 12) in three or more. Three tasks were impaired in at least 19-20% of RRMS group, namely the emotional question of the Faux Pas task, the violation of norms of the Social Situation Test and the recognition of sadness and anger of the Emotion Attribution Test. In particular, one third of patients failed in identifying anger situations described in the stories. The proportions of impaired RRMS subjects were computed for significant domains of social cognition and ToM (Faux Pas Test, recognition of sadness and anger, and violation of norms) (**Figure 8B**).

	RRMS (n. 42)	HC (n. 30)
Faux Pas Test global score (0-40)	36.7 ± 3.7	38.5 ± 2.4
- Detection question (0-10)	9.4 ± 0.8	9.8 ± 0.5
- False belief question (0-10)	9.3 ± 1	9.7 ± 0.6
- Unintentional question (0-10)	8.7 ± 1.5	9.4 ± 1.1
- Emotional question (0-10)	9.2 ± 0.9	9.6 ± 0.7
Theory of Mind Test (max13)	12.8 ± 0.6	12.9 ± 0.3
Social Situation Test		
- No. of normative behaviours (max15)	13.9 ± 1.5	14.2 ± 0.8
- No. of norm violation (max25)	23.1 ± 2	23.5 ± 1.2
- Violations degree (max75)	51.2 ± 9.1	50 ± 7
Emotions Attribution Test		
- Sadness (max10)	**7.5[a] ± 1.6**	9 ± 1.2
- Fear (max10)	9.2 ± 1.1	9.1 ± 1.1
- Embarrassment (max12)	10.1 ± 1.9	11 ± 1.1
- Disgust (max3)	2.8 ± 0.4	2.9 ± 0.3
- Happiness (max10)	9.7 ± 0.7	9.8 ± 0.6
- Anger (max10)	**7.7[a] ± 2.2**	9.3 ± 0.9
- Envy (max3)	2.5 ± 0.9	2.7 ± 0.5

Table 4B. Raw mean scores of social cognition tests obtained by patients with relapsing-remitting multiple sclerosis and healthy controls; $p < 0.001$ versus [a]HC

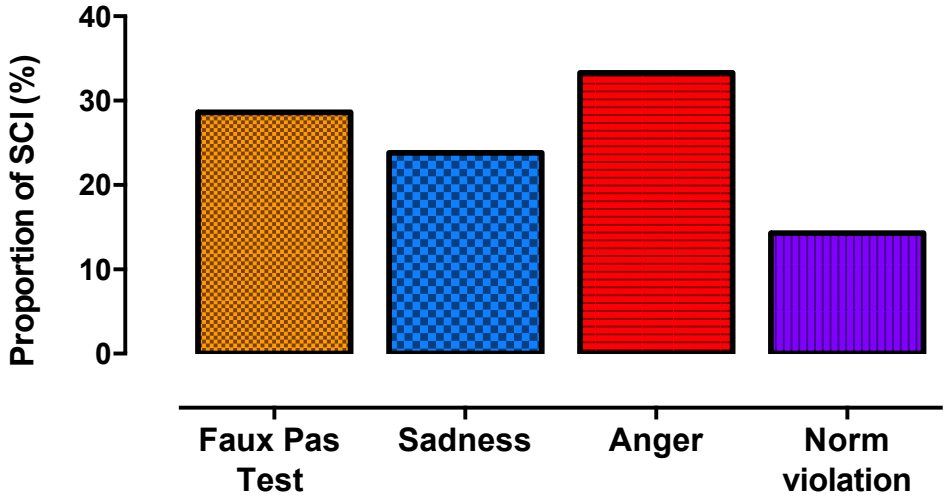

Figure 8B. Proportion of relapsing-remitting multiple sclerosis patients with impaired social cognition; SCI, social cognitive impairment

Emotional-behavioral questionnaire results

Mean comparison of emotional and behavioral characteristics of patients and controls is presented in **Table 4C**. There was no significant difference on the BDI, STAI-X1 and STAI-X2 questionnaires and on some subscales (INT, DEP, ANX, PHOB, PSY) of the SCL-90.

Mann-Whitney test revealed that, compared to healthy subjects, patients had worse scores only on the SCL-90 scales (SOM, O-C, HOS, PAR, GSI). In the RRMS group, mean scores did not exceed the literature cut-off values for fatigue on MFIS. Patients also showed high scores in both physical and mental health of the MSQOL-54.

	RRMS (n. 42)	HC (n. 30)
BDI	6.7 ± 6.2	3.6 ± 2.6
STAI-X1	33.9 ± 7.8	28.7 ± 5.3
STAI-X2	36.3 ± 9.1	33.4 ± 8.2
MFIS	19.4 ± 13.7	–
MSQOL-54		
- Physical Health	78.7 ± 12.4	–
- Mental Health	74.8 ± 13.5	–
SCL-90		
- Somatization	**0.7[a] ± 0.5**	0.3 ± 0.2
- Obsessive-Compulsive	**0.8[a] ± 0.7**	0.3 ± 0.3
- Interpersonal Sensitivity	0.4 ± 0.5	0.2 ± 0.3
- Depression	0.6 ± 0.5	0.3 ± 0.2
- Anxiety	0.5 ± 0.4	0.3 ± 0.3
- Hostility	**0.4[a] ± 0.5**	0.1 ± 0.2
- Phobic Anxiety	0.1 ± 0.1	0.1 ± 0.1
- Psychoticism	0.3 ± 0.4	0.1 ± 0.2
- Paranoid Ideation	**0.5[a] ± 0.5**	0.1 ± 0.2
- Global Severity Index	**0.5[a] ± 0.4**	0.2 ± 0.1

Table 4C. Raw mean scores of emotional-behavioral questionnaires obtained by patients with relapsing-remitting multiple sclerosis and healthy controls; BDI, Beck Depression Inventory; STAI-X, State-Trait Anxiety Inventory; MFIS, Modified Fatigue Impact Scale; MSQOL, Multiple Sclerosis Quality of Life; SCL, Symptom Checklist; $p \leq 0.001$ versus [a]HC

MRI data results

Group comparison assessing the baseline volume between 38 RRMS patients and 17 MRI controls failed to detect statistical volume variations either in the whole brain (patients, M = 1364.5, SD = 114.4; controls, M = 1370.4, SD = 125.9) or in the WM (patients, M = 556.1, SD = 62.9; controls, M = 567, SD = 67.7). In contrast, VMB analysis revealed a minimal but significant reduction in regional GM density in patients (M = 593.8, SD = 52.6) compared to controls (M = 592.7, SD = 61.3), which met both criteria of $p < 0.005$ and minimum extent of 100 voxels. AAL tool, used for the anatomical labeling of functional brain mapping, identified two major clusters (**Figure 9**). The first with a borderline significance (x, y, z = -39, 2, 7; 256 voxels) and AVOI in the left insula (t = 4.74, 1858 voxels, 3.8% label) and putamen (t = 4.08, 1009 voxels, 1.1% label). The second cluster (x, y, z = 29, 11, -48; 945 voxels) had its peak of significance in the right hemisphere with AVOI in the middle temporal gyrus-pole (i.e., including the anatomical portion of the temporal pole adjacent to the middle temporal gyrus) (t = 4.54, 1187 voxels, 14.2% label) and inferior temporal gyrus (t = 4.40, 3357 voxels, 4.3% label) (**Table 5A**). In the regression model, only age and sex were retained when predicting the GM volume, which accounted for 53% of the variance (**Table 5B**). A further analysis was conducted to deepen the differences in age and gender in the RRMS group. Patients were arbitrarily divided into two age-groups, young (18-35 years) and old (36-50 years), respectively. Results showed that older patients had a significantly lower GM volume than younger ones. With regard to gender, women had a reduced but not significant GM volume compared to men (**Table 5C**).

There were no other significant variables among the selected cognitive (Verbal Memory, Visuospatial Memory, Non-speeded Executive Functions, Speeded Executive Functions, Visual Skills), socio-demographic (education level) and clinical (disease duration, EDSS) measures, whose correlations are reported in **Table 5D**.

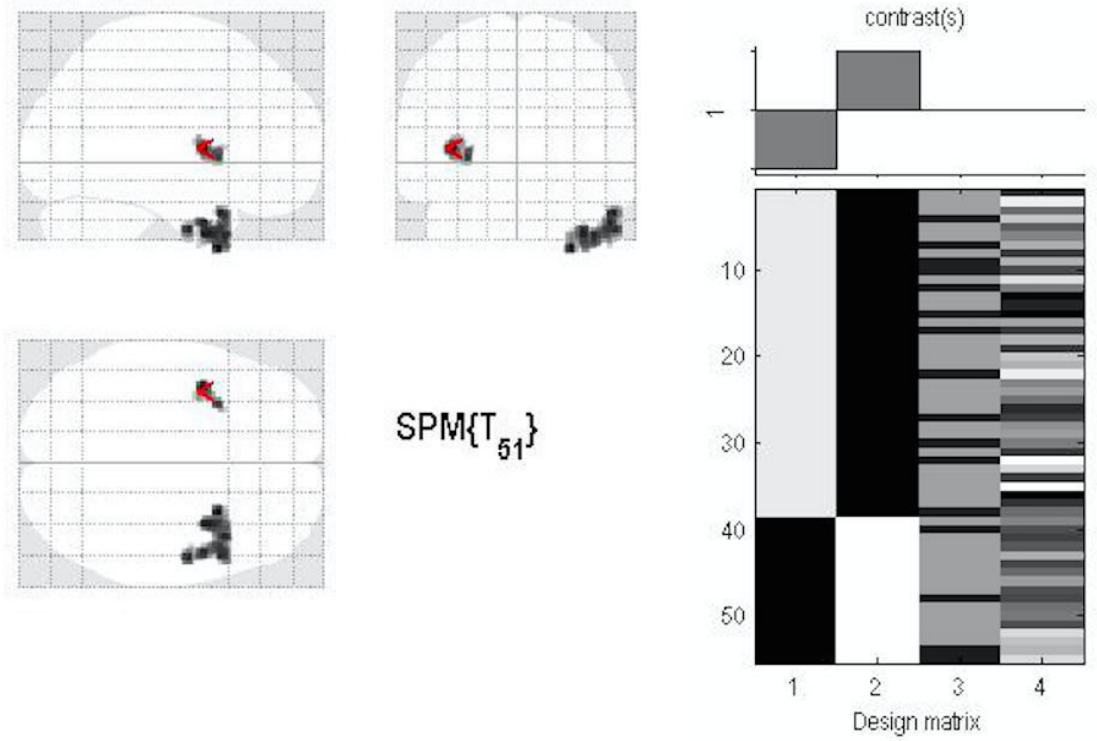

Figure 9. Significant difference in gray matter regions between patients and controls identified by two main clusters.

	Talairach Coordinates							
	x	*y*	*z*	*Z scores*	*x*	*y*	*z*	*Z scores*
Brain area	**Left hemisphere**				**Right hemisphere**			
Insula	-39	2	7	4.30				
Putamen	-30	11	1	3.78				
Middle temporal gyrus-pole					29	11	-48	4.14
Inferior temporal gyrus					36	3	-41	4.03

Table 5A. Main group effect on cortical and deep gray matter in patients with relapsing-remitting multiple sclerosis.

	R^2	Change R^2	Standardized coefficient (β)	F	P value
Age	0.342	0.324	-0.585	18.746	0.000
Age, sex	0.526	0.499	-0.622, -0.430	19.419	0.000

Table 5B. Stepwise linear regression analysis on the gray matter volume in patients with relapsing-remitting multiple sclerosis.

	Age-groups		Sex	
	18-35 (n. 22)	36-55 (n. 16)	Men (n. 12)	Women (n. 26)
GM volume	**621.4 ± 43.1**	**555.9 ± 39.7**	622.6 ± 56.2	580.6 ± 46.1

Table 5C. Age and sex differences on gray matter volume in patients with relapsing-remitting multiple sclerosis; in bold $p < 0.001$

	GM volume	Sex	Age	Education level	EDSS	Disease duration	Verbal Memory	Visuospatial Memory	Non-speeded EF	Speeded EF	Visual Skills
GM volume	1	-0.38	**-0.59***	-0.10	0.19	0.18	0.10	0.33	0.15	0.27	-0.15
Sig.(one-tailed)	–	0.10	0.00	0.27	0.13	0.14	0.28	0.02	0.18	0.05	0.18
Sex		1	-0.09	0.16	-0.15	-0.30	0.33	-0.11	-0.18	0.05	**0.46***
Sig.(one-tailed)		–	0.30	0.18	0.18	0.03	0.02	0.26	0.14	0.38	0.00
Age			1	0.20	0.12	-0.15	-0.15	-0.33	-0.60	-0.15	0.06
Sig.(one-tailed)			–	0.11	0.23	0.18	0.19	0.02	0.37	0.18	0.36
Education level				1	-0.21	0.09	0.37	0.30	-0.15	**0.51***	0.12
Sig.(one-tailed)				–	0.10	0.30	0.01	0.03	0.19	0.00	0.24
EDSS					1	-0.11	-0.25	-0.22	-0.12	-0.23	-0.10
Sig.(one-tailed)					–	0.26	0.07	0.09	0.23	0.08	0.31
Disease duration						1	0.13	0.25	0.03	0.03	-0.08
Sig.(one-tailed)						–	0.23	0.06	0.42	0.43	0.31
Verbal Memory							1	**0.45***	-0.02	**0.62***	0.38
Sig.(one-tailed)							–	0.00	0.46	0.00	0.01
Visuospatial Memory								1	0.21	**0.70***	0.07
Sig.(one-tailed)								–	0.10	0.00	0.35
Non-speeded EF									1	-0.06	-0.07
Sig.(one-tailed)									–	0.37	0.35
Speeded EF										1	0.15
Sig.(one-tailed)										–	0.18
Visual Skills											1
Sig.(one-tailed)											–

Table 5D. Pearson's correlation between variables of the linear regression model in patients with relapsing-remitting multiple sclerosis; GM, gray matter, EDSS, Expanded Disability Status Scale; EF, executive functions; *$p \leq 0.002$

Correlation analysis between MRI and cognitive measures

Correlation analysis showed significant associations between cognitive measures and GM/WM regions, all of which were positively correlated.

As for the relationship between processing speed, working memory and executive tests and GM structures (**Table 6A**), we found the following: SDMT was correlated with one cluster (x, y, z = 3, -12, 12; 338 voxels) that identified a consistent outside area (i.e., part of the region outside of the parcellation), followed by the right thalamus (t = 3.51, 1057 voxels, 6.6% label); PASAT-2 with a single cluster (x, y, z = 45, 23, 3; 295 voxels) and AVOI in the right triangular inferior frontal gyrus (t = 4.77, 2151 voxels, 2.5% label), insula (t = 3.74, 1770 voxels, 2.5% label) and inferior frontal operculum (t = 3.22, 1399 voxels, 1.6% label). Furthermore, phonemic fluency was related to one cluster with borderline significance (x, y, z = 51, -33, 45; 228 voxels) and was localized in the right parietal lobe including the supramarginal (t = 3.89, 1974 voxels, 2.6% label) and postcentral gyri (t = 3.56, 3823 voxels, 1.2% label); backward digit span was correlated with one cluster (x, y, z = 30, -9, 21; 237 voxels) in the right hippocampus (t = 4.37, 946 voxels, 6.7% label), amygdala (t = 3.38, 248 voxels, 3.7% label) and parahippocampal gyrus (t = 4.12, 1132 voxels, 1% label); backward Corsi block correlations identified a first cluster (x, y, z = -36, -82, 36; 396 voxels) with AVOI in the left middle occipital lobe (t = 4.30, 3270 voxels, 4.7% label), and a second cluster (x, y, z = 45, -24, 24; 393 voxels) in the right Rolandic operculum (t = 4.29, 1331 voxels, 3.9% label), insula (t = 3.72, 1770 voxels, 1.9% label) and Heschl gyrus (t = 3.54, 249 voxels, 12.9% label).

Cognitive measure	Cerebral region	Side (Right/Left)	Talairach Coordinates			Z scores
			x	y	z	
SDMT	Thalamus	R	6	-3	9	3.19
PASAT-2	Inferior frontal gyrus, triangular	R	45	23	3	4.08
	Insula	R	48	14	1	3.36
	Inferior frontal gyrus, opercular	R	36	26	4	2.96
Phonemic fluency	Supramarginal gyrus	R	51	-33	45	3.48
	Postcentral gyrus	R	59	-19	40	3.23
Digit span backward	Hippocampus	R	30	-9	21	3.82
	Amygdala	R	35	-15	-27	3.09
	Parahippocampal gyrus	R	35	-3	26	3.64
Corsi block backward	Middle occipital lobe	L	-36	-82	36	3.76
	Rolandic operculum	R	45	-24	24	3.76
	Insula	R	33	-25	9	3.35
	Heschl gyrus	R	38	-25	19	3.21

Table 6A. Correlation analysis between gray matter regions and processing speed, working memory and executive measures in patients with relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; PASAT-2, Paced Auditory Serial Addition Test, 2-sec trial

Correlations with memory and social cognition measures are reported in **Table 6B**. Regarding memory tests, we found significant relationships between SRT-D e SPART-D and several GM regions. In particular, SRT-D was associated with four clusters: the first (x, y, z = -33, -76, -45; 428 voxels) included AVOI in the left cerebellum Crus II and lobule VII (t = 4.79, 1894 voxels, 9% label; t = 3.98, 585 voxels, 1.3% label); the second with a borderline significance (x, y, z = 51, 20, 9; 219 voxels) consisted of the right triangular and opercular inferior frontal gyrus (t = 4.34, 2151 voxels, 3.3% label; t = 3.62, 1399 voxels, 1.6% label); the third (x, y, z = 29, -79, -44; 330 voxels) included two right cerebellar regions, i.e. Crus II and lobule VII (t = 4.05, 2117 voxels, 5.6% label; t = 3.93, 534 voxels, 2.4% label); the fourth (x, y, z = 11, -30, 2; 341 voxels) only the right thalamus (t = 3.54, 1057 voxels, 10.6% label). Correlations with SPART-D highlighted three clusters. The first (x, y, z = -48, -3, -26; 308 voxels) was located in the left hemisphere and included the middle temporal gyrus (t = 5.96, 4942 voxels, 1.8% label) and superior and middle temporal gyrus-pole (t = 4.54, 1285 voxels, 2.7% label; t = 3.47, 755 voxels, 1% label). Conversely, the second cluster (x, y, z = 50, 3, -17; 717 voxels) consisted of the right superior and middle temporal gyrus (t = 4.47, 3141 voxels, 4% label; t = 4.36, 4409 voxels, 2.6% label) and superior temporal gyrus-pole (t = 4.18, 1338 voxels, 1.4% label). The third cluster (x, y, z = -32, -4, 10; 331 voxels) included the left insula and Rolandic operculum (t = 3.76, 1858 voxels, 4.2% label; t = 3.56, 990 voxels, 5% label).

With regards to the social cognition measures, only sadness of the Emotion Attribution Test showed a significant relationship with GM cluster (x, y, z = -3, 32, 21; 245 voxels), which was located in the left anterior cingulum (t = 4.81, 1400 voxels, 7.1% label).

Cognitive measure	Cerebral region	Side (Right/Left)	Talairach Coordinates			Z scores
			x	y	z	
SRT-D	Cerebellum Crus II	L	-33	-76	-45	4.10
	Cerebellum VII	L	-23	-78	-44	3.54
	Inferior frontal gyrus, triangular	R	51	20	9	3.79
	Inferior frontal gyrus, opercular	R	57	24	3	3.27
	Cerebellum Crus II	R	29	-79	-44	3.59
	Cerebellum VII	R	24	-85	-41	3.50
	Thalamus	R	11	-30	-2	3.48
SPART-D	Middle temporal gyrus	L	-48	-3	26	4.80
	Superior temporal gyrus-pole	L	-44	9	-24	3.93
	Middle temporal gyrus-pole	L	-48	8	17	3.15
	Superior temporal gyrus	R	50	3	-17	3.88
	Middle temporal gyrus	R	59	-27	-3	3.81
	Superior temporal gyrus-pole	R	48	-22	-12	3.68
	Insula	L	-32	-4	10	3.37
	Rolandic operculum	L	-45	-6	9	3.23
Sadness	Anterior cingulum	L	-3	32	21	4.11

Table 6B. Correlation analysis between gray matter regions and memory measures and sadness in patients with relapsing-remitting multiple sclerosis; SRT-D, Selective Reminding Test, delay recall; SPART-D, Spatial Recall Test, delay recall

As for WM regions, correlation analysis revealed a significant association only with executive and processing speed measures, namely SDMT, PASAT-2 and Stroop test (**Table 6C**). SDMT was associated with three clusters, all identified by consistent outside areas. The first (x, y, z = -41, -40, 30; 645 voxels) was located in the left parietal supramarginal gyrus (t = 3.64, 1256 voxels, 3.3% label); the remaining clusters covered a large portion of both temporal lobes (left, x, y, z = -24, -28, 2; 835 voxels; right, x, y, z = 30, -30, 5; 489 voxels) with AVOI in the left thalamus (t = 3.72, 1100 voxels, 4% label) and the two hippocampi (left, t = 3.75, 932 voxels, 10.8% label; right, t = 3.15, 946 voxels, 6.4% label). PASAT-2 was related to one cluster identified by a large outside region (x, y, z = 38, 2, -35; 562 voxels), involving the right middle temporal gyrus-pole and inferior temporal gyrus (t = 3.67, 1187 voxels, 3.1% label; t = 4.18, 3357 voxels, 1.9% label). Finally, the Stroop test was correlated with a single cluster (x, y, z = 56, -12, 19; 373 voxels) in the right postcentral gyrus and Rolandic operculum (t = 5.10, 3823 voxels, 1.6% label; t = 2.96, 1331 voxels, 3.1% label).

Cognitive measure	Cerebral region	Side (Right/Left)	Talairach Coordinates			Z scores
			x	y	z	
SDMT	Supramarginal gyrus	L	-50	-39	42	3.28
	Hippocampus	L	-29	-21	-11	3.37
	Thalamus	L	-18	-34	3	3.35
	Hippocampus	R	33	-16	-5	2.91
PASAT-2	Middle temporal gyrus-pole	R	45	-1	-20	3.31
	Inferior temporal gyrus	R	51	-13	-23	3.68
Stroop	Postcentral gyrus	R	56	-12	19	4.29
	Rolandic operculum	R	44	-18	22	2.75

Table 6C. Correlation analysis between white matter regions and executive and processing speed measures in patients with relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; PASAT-2, Paced Auditory Serial Addition Test, 2-sec trial

3.3.3 Follow-up data

Neuropsychological test results

Considering the comparison with healthy subjects at the single time-point, overall RRMS group performance improved over time, with some exceptions (**Table 7A**). After six months, significant differences in the backward digit span and Corsi block, Stroop task and phonemic fluency were retained, while in the immediate and delay recall of the SPART, brief story recall, Street test and 2-sec PASAT they had disappeared. After one year, patients had also significantly improved in the phonemic fluency, but they were significantly impaired in the forward digit span and Corsi block, compared to controls. Performance on the backward digit span, backward Corsi block and Stroop test were not significantly changed.

ANOVA with repeated measures was performed to control for possible bias due to learning effects in RRMS group. Post-hoc tests are shown in **Table 7A**. Analyses revealed a significant time effect in the following measures: LTS and CLTS subscales of the SRT, SPART, SDMT, PASAT-3, PASAT-2, brief story recall, ROCF-delay recall, phonemic fluency, and Street test. There was no significant effect in the SRT-D, SPART-D, forward and backward digit span and Corsi block, ROCF-copy, Stroop task, semantic fluency, FAB, and all subscores (global score, perseverative and non-perseverative errors, failure to maintain set) of the WCST.

Considering baseline measures, those that were significantly worse than both six-month and one-year follow-ups included the SRT-LTS, brief story recall, ROCF-delay recall, 3-sec and 2-sec PASAT. SRT-CLTR, SPART immediate recall and SDMT were impaired only compared to the six-month follow-up, whereas Street task and phonemic fluency were significantly worse only than the one-year evaluation. After six months, SRT-CLTR, SPART immediate recall and SDMT were significantly improved. Performance on brief story recall and phonemic fluency were still significantly worse between six months and one-year follow-ups. One-year evaluation showed a significant improvement on the Street test only with respect to baseline, while mean scores on SRT-LTS, ROCF-delay recall, 3-sec and 2-sec PASAT were significantly better compared to both baseline and six-month measurements. Performance on brief story recall and phonemic fluency

were no longer impaired, while forward digit span and Corsi block had worsened between the baseline and one-year measurements.

	RRMS (n. 42)			HC (n. 30)
	Baseline (T0)	Six months (T1)	One year (T2)	
Selective Reminding Test				
- Long Term Storage	**51.9[c,d] ± 14.9**	57.5 ± 16.7	59.8 ± 13.4	61.6 ± 12.5
- Consistent Long Term Retrieval	**45.8[c] ± 18.7**	52.7 ± 20.2	54.3 ± 18.6	57.6 ± 16.2
- Delay Recall	9.3 ± 2.4	10 ± 2.1	10.4 ± 1.9	10.7 ± 1.5
Spatial Recall Test				
- Immediate Recall	**20.4[a,c] ± 5.3**	23.5 ± 3.8	22.5 ± 5.5	25.2 ± 3.6
- Delay Recall	**7.4[a] ± 2.2**	8 ± 2.2	8.9 ± 1.6	8.9 ± 1.6
Digit span, forward	6.3 ± 1	6.3 ± 1.1	**5.8[a] ± 1**	6.8 ± 0.9
Digit span, backward	**4.6[a] ± 0.9**	**4.8[a] ± 1.3**	**4.9[a] ± 1.1**	5.8 ± 1.1
Corsi block, forward	5.7 ± 1.1	5.7 ± 1.1	**5.6[a] ± 1**	6.5 ± 1
Corsi block, backward	**5.1[a] ± 1**	**5.1[a] ± 1.2**	**5[a] ± 1.1**	6 ± 1.1
Brief story recall	**15.3[a,c,d] ± 3.5**	**17.6[d] ± 3.9**	19.4 ± 4.1	20.3 ± 3.9
Rey-Osterrieth Complex Figure				
- Copy	35.1 ± 1.2	34.5 ± 2.4	34.8 ± 1.5	35.4 ± 0.9
- Delay Recall	**21.3[c,d] ± 5.2**	23.6 ± 4.6	24 ± 4.8	24.1 ± 4.9
Street's Completion Test	**9.2[a,d] ± 1.9**	9.8 ± 1.9	10 ± 1.5	10.6 ± 1.5
Stroop Colour-Word Test	**30.6[a] ± 6.8**	**31.1[a] ± 7.1**	**31.8[a] ± 6**	38.1 ± 6
Phonemic fluency	**37.3[a,d] ± 7.6**	**37.8[a,d] ± 8.8**	41.7 ± 10.2	45.8 ± 9.3
Semantic fluency	47.4 ± 7.9	47.7 ± 9.2	49.1 ± 8.1	50.3 ± 7.7
Symbol Digit Modalities Test	**57.1[c] ± 12.4**	60.5 ± 12.2	59.9 ± 14	64.1 ± 12.6
Paced Auditory Serial Addition Test				
- 3 sec trial	**45.6[c,d] ± 10**	49 ± 9	49.5 ± 8.8	52.1 ± 7.5
- 2 sec trial	**34.5[a,c,d] ± 11.5**	38.7 ± 10.8	40.3 ± 11	43.4 ± 11.5
Frontal Assessment Battery	17.7 ± 0.6	17.6 ± 0.7	17.6 ± 0.7	17.8 ± 0.5
Wisconsin Card Sorting Test				
- Global score	15.5 ± 7	17 ± 10.9	14.9 ± 7.3	14.2 ± 6
- Perseverative errors	6.4 ± 2.3	6.6 ± 2.9	5.4 ± 1.8	5.3 ± 1.5
- Non-perseverative errors	4 ± 2.2	3.6 ± 1.5	3.9 ± 1.8	3.8 ± 1.8
- Failure to maintain set	0.3 ± 0.6	0.4 ± 1	0.4 ± 0.7	0.1 ± 0.3

Table 7A. Raw mean scores of cognitive tests obtained by patients with relapsing-remitting multiple sclerosis at baseline, six-month and one-year follow-ups, and healthy controls; $p \leq 0.002$ versus [a]HC, [b]T0, [c]T1, [d]T2

Social cognition measure results

After one year, the average scores of the RRMS group in social cognition and ToM measures had also improved, with the two exceptions in the Emotion Attribution Test (**Table 7B**). Wilcoxon test showed that the recognition of sadness had significantly worsened between the baseline and follow-up measurements. In contrast, the attribution of anger had significantly improved. Compared to healthy subjects, sadness was further impaired after one year, while anger no longer showed any significant difference.

	RRMS (n. 42)		HC (n. 30)
	Baseline (T0)	One year (T1)	
Faux Pas Test global score (0-40)	36.7 ± 3.7	36.4 ± 5.8	38.5 ± 2.4
- Detection question (0-10)	9.4 ± 0.8	9.5 ± 0.8	9.8 ± 0.5
- False belief question (0-10)	9.3 ± 1	9.4 ± 1.1	9.7 ± 0.6
- Unintentional question (0-10)	8.7 ± 1.5	9 ± 1.5	9.4 ± 1.1
- Emotional question (0-10)	9.2 ± 0.9	9.3 ± 0.9	9.6 ± 0.7
Theory of Mind Test (max13)	12.8 ± 0.6	12.08 ± 0.6	12.9 ± 0.3
Social Situation Test			
- No. of normative behaviours (max15)	13.9 ± 1.5	13.9 ± 1.9	14.2 ± 0.8
- No. of norm violation (max25)	23.1 ± 2	23.4 ± 1.4	23.5 ± 1.2
- Violations degree (max75)	51.2 ± 9.1	50.9 ± 7.5	50 ± 7
Emotions Attribution Test			
- Sadness (max10)	**7.5[a] ± 1.6**	**6.6[a,b] ± 1.5**	9 ± 1.2
- Fear (max10)	9.2 ± 1.1	9.4 ± 0.8	9.1 ± 1.1
- Embarrassment (max12)	10.1 ± 1.9	10.9 ± 1.7	11 ± 1.1
- Disgust (max3)	2.8 ± 0.4	2.9 ± 0.2	2.9 ± 0.3
- Happiness (max10)	9.7 ± 0.7	9.8 ± 0.2	9.8 ± 0.6
- Anger (max10)	**7.7[a,c] ± 2.2**	9.1 ± 1.6	9.3 ± 0.9
- Envy (max3)	2.5 ± 0.9	2.8 ± 0.5	2.7 ± 0.5

Table 7B. Raw mean scores of social cognition tests obtained by patients with relapsing-remitting multiple sclerosis at the baseline and after one year, and healthy controls; $p \leq 0.001$ versus [a]HC, [b]T0, [c]T1

Taking into consideration the composite scores of cognitive measures, after six months 57.1% (N. 24) of the RRMS group showed no impairment on any test, 19% (N. 8) was compromised on one test, 16.7% (N. 7) on two, and 7.2% (N. 3) on three or more. After one year, 61.9% (N. 26) showed no abnormal scores, 7.2% (N. 3) was impaired in one test, 11.9% (N. 5) in two, and 19% (N. 8) in three or more.

Regarding tasks of social cognition, after one year 73.8% (N. 31) of patients showed no abnormal score, 11.9% (N. 5) were compromised on one measure, 4.8% (N. 2) on two, and 9.5% (N. 4) on three or more.

The proportions of patients and the related trend of cognitive and social cognition impairment between baseline and different time-points are presented in **Figure 10**.

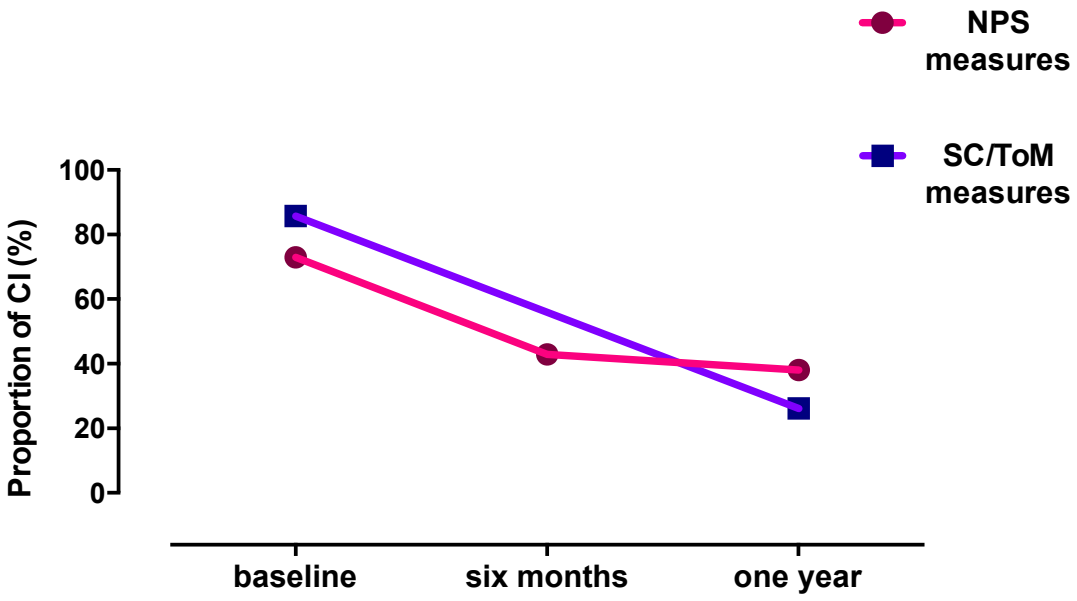

Figure 10. Proportion of relapsing-remitting multiple sclerosis patients with impaired social and non-social cognition; CI, cognitive impairment; NPS, neuropsychological; SC/ToM, social cognition/theory of mind

Emotional-behavioral questionnaire results

Overall, the mean scores of mood, fatigue and quality of life questionnaires remained stable after one year. The only difference concerned the SCL-90 scale (**Table 7C**).

The Wilcoxon analysis showed no significant difference between the first and second evaluations in the observed measures.

As for the comparison with healthy subjects, Mann-Whitney test revealed a significant difference between patients and controls on SCL-90 DEP and GSI subscales. While overall severity was slightly but not statistically improved, depression had significantly worsened after one year. Conversely, measures of SOM, O-C, HOS, and PAR were no longer significantly different between the two groups at follow-up.

	RRMS (n. 42)		HC (n. 30)
	Baseline (T0)	One year (T1)	
BDI	6.7 ± 6.2	6.8 ± 6	3.6 ± 2.6
STAI-X1	33.9 ± 7.8	33.5 ± 6.9	28.7 ± 5.3
STAI-X2	36.3 ± 9.1	36.6 ± 9.5	33.4 ± 8.2
MFIS	19.4 ± 13.7	19 ± 15.1	–
MSQOL-54			
- Physical Health	78.7 ± 12.4	78.1 ± 14.4	–
- Mental Health	74.8 ± 13.5	75.5 ± 13.3	–
SCL-90			
- Somatization	**0.7[a] ± 0.5**	0.6 ± 0.5	0.3 ± 0.2
- Obsessive-Compulsive	**0.8[a] ± 0.7**	0.6 ± 0.6	0.3 ± 0.3
- Interpersonal Sensitivity	0.4 ± 0.5	0.3 ± 0.3	0.2 ± 0.3
- Depression	0.6 ± 0.5	**1.1[a] ± 1**	0.3 ± 0.2
- Anxiety	0.5 ± 0.4	0.6 ± 0.5	0.3 ± 0.3
- Hostility	**0.4[a] ± 0.5**	0.4 ± 0.5	0.1 ± 0.2
- Phobic Anxiety	0.1 ± 0.1	0.9 ± 0.2	0.1 ± 0.1
- Psychoticism	0.3 ± 0.4	0.2 ± 0.3	0.1 ± 0.2
- Paranoid Ideation	**0.5[a] ± 0.5**	0.4 ± 0.5	0.1 ± 0.2
- Global Severity Index	**0.5[a] ± 0.4**	**0.4[a] ± 0.4**	0.2 ± 0.1

Table 7C. Raw mean scores of emotional-behavioral questionnaires obtained by patients with relapsing-remitting multiple sclerosis at the baseline and after one year, and healthy controls; BDI, Beck Depression Inventory; STAI-X, State-Trait Anxiety Inventory; MFIS, Modified Fatigue Impact Scale; MSQOL, Multiple Sclerosis Quality of Life; SCL, Symptom Checklist; $p \leq 0.002$ versus [a]HC

MRI data results

Paired data test failed to detect any statistical variation in the total brain or WM volumes between the first and second MRI measurements in RRMS group. Again, volumetric analysis revealed minimal but significant morphological differences in GM volume between patients and controls (**Table 8A**). AAL tool identified four main clusters (**Figure 11**). The first (x, y, z = 36, 9, -42; 467 voxels) had its peak of significance in the right inferior temporal gyrus (t = 4.23, 3557 voxels, 2.4% label), followed by the right middle temporal gyrus-pole (t = 3.78, 1187 voxels, 6.5% label). The second cluster had a borderline significance (x, y, z = 24, 8, -15; 253 voxels) and AVOI in the right amygdala (t = 4.15, 248 voxels, 4.9% label), putamen (t = 3.46, 1064 voxels, 1% label) and globus pallidus (t = 3.22, 280 voxels, 2.3% label). The last two clusters involved both cerebellar hemispheres. The third (x, y, z = -11, -87, -33; 398 voxels) with AVOI in the left Crus II (t = 3.53, 1894 voxels, 7.9% label) and the fourth (x, y, z = 12, -87, -35; 338 voxels) in the right Crus II and I (t = 3.31, 2117 voxels, 4.5% label; t = 3.28, 2648 voxels, 1.8% label) (**Table 8B)**.

	RRMS		HC
	Baseline (n. 38)	One year (n.30)	(n. 17)
Total volume (cc)	1364.5 ± 114.4	1374.6 ± 116.7	1370.4 ± 125.9
GM volume (cc)	**593.8[a] ± 52.6**	**592.4[a] ± 50**	592.7 ± 61.3
WM volume (cc)	556.1 ± 62.9	565.4 ± 65.6	567 ± 67.7

Table 8A. Average volume of total brain, white and gray matter of patients with relapsing-remitting multiple sclerosis and healthy controls; $p < 0.005$ versus [a]HC

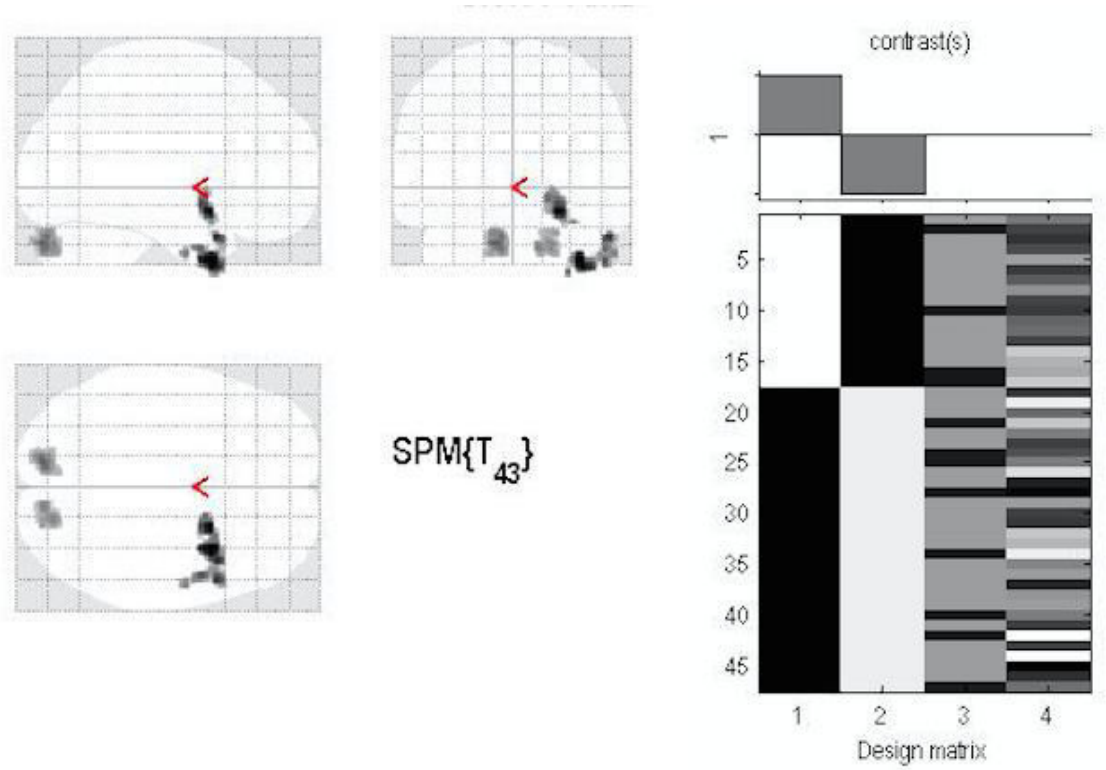

Figure 11. Significant difference in gray matter regions between patients and controls identified by four main clusters.

	Talairach Coordinates							
	x	*y*	*z*	*Z scores*	*x*	*y*	*z*	*Z scores*
Brain area	**Left hemisphere**				**Right hemisphere**			
Inferior temporal gyrus					36	9	-42	3.85
Middle temporal gyrus-pole					53	12	-29	3.50
Amygdala					24	8	-15	3.79
Putamen					18	5	-8	2.23
Globus pallidus					33	9	-21	3.22
Cerebellum Crus II	-11	-87	-33	3.29				
Cerebellum Crus II					12	-87	-35	3.10
Cerebellum Crus I					21	-81	-33	3.08

Table 8B. Main group effect on cortical and deep gray matter in patients with relapsing-remitting multiple sclerosis.

In the regression model, sex, age and Speeded Executive Functions accounted for 64% of the variance in predicting the GM volume at one-year follow-up in the RRMS group (**Table 8C**). The same analysis performed for baseline data was conducted to investigate age and gender differences. Again, patients in the 36-50 age-group had a significantly reduced GM volume compared to 18-35 age-group. In addition, gender also revealed a significant difference, showing that women had a statistically lower GM volume than men (**Table 8D**).

A further stepwise regression with the same modality was carried out to determine which cognitive measure within the Speeded EF domain was able to predict the GM volume at follow-up. Analysis revealed significant contributions from sex, age and SDMT as independent predictors of GM volume, which accounted for 59% of the variance (**Table 8E**). No effect was found among the other measures. Correlations between cognitive, socio-demographic and clinical variables and GM volume are shown in **Table 8F**.

	R^2	Change R^2	Standardized coefficient (β)	F	P value
Sex	0.271	0.245	-0.520	10.387	0.003
Sex, age	0.567	0.535	-0.560, -0.546	17.702	0.000
Sex, age, Speeded EF	0.640	0.599	-0.556, -0.510, 0.273	15.432	0.000

Table 8C. Stepwise linear regression analysis on the gray matter volume in patients with relapsing-remitting multiple sclerosis; Speeded EF, Speeded Executive Functions

	Age-groups		Sex	
	18-35 (n. 18)	36-55 (n. 12)	Men (n. 9)	Women (n. 21)
GM volume	**615.5[a] ± 46.8**	**557.8 ± 32**	**631.4[b] ± 44.5**	**575.7 ± 43**

Table 8D. Age and sex differences on gray matter volume in patients with relapsing-remitting multiple sclerosis; in bold $^{a}p = 0.001$, $^{b}p = 0.003$

	R^2	Change R^2	Standardized coefficient (β)	F	P value
Sex	0.271	0.245	-0.520	10.387	0.003
Sex, age	0.567	0.535	-0.560, -0.546	17.702	0.000
Sex, age, SDMT	0.635	0.593	-0.567, -0.432, 0.285	15.104	0.000

Table 8E. Stepwise linear regression analysis on the gray matter volume in patients with relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test

	GM volume	Sex	Age	Education level	EDSS	Disease duration	SDMT	PASAT-3	PASAT-2	Stroop	Phonemic fluency
GM volume	1	**-0.52***	**-0.51***	-0.18	0.16	0.19	0.43	0.30	0.39	0.19	0.30
Sig.(one-tailed)	–	0.00	0.00	0.17	0.21	0.16	0.01	0.05	0.02	0.15	0.44
Sex		1	-0.07	0.21	-0.16	-0.47	0.05	-0.19	-0.22	0.16	0.26
Sig.(one-tailed)		–	0.35	0.13	0.20	0.10	0.39	0.16	0.12	0.20	0.08
Age			1	0.28	0.13	-0.04	-0.40	0.02	-0. 02	-0.37	0.12
Sig.(one-tailed)			–	0.07	0.25	0.42	0.01	0.46	0.46	0.02	0.26
Education level				1	-0.25	0.04	0.33	**0.54***	0.44	0.22	**0.51***
Sig.(one-tailed)				–	0.09	0.41	0.04	0.00	0.00	0.12	0.00
EDSS					1	-0.09	-0.13	0.04	0.10	-0.31	-0.11
Sig.(one-tailed)					–	0.32	0.25	0.42	0.49	0.47	0.47
Disease duration						1	0.13	0.05	-0.01	-0.02	-0.02
Sig.(one-tailed)						–	0.25	0.41	0.49	0.47	0.47
SDMT							1	**0.56***	**0.57***	**0.72***	0.46
Sig.(one-tailed)							–	0.00	0.00	0.00	0.01
PASAT-3								1	**0.87***	**0.51***	0.40
Sig.(one-tailed)								–	0.00	0.00	0.02
PASAT-2									1	0.50*	0.39
Sig.(one-tailed)									–	0.00	0.02
Stroop										1	0.36
Sig.(one-tailed)										–	0.03
Phonemic fluency											1
Sig.(one-tailed)											–

Table 8F. Pearson's correlation between variables of the linear regression model in patients with relapsing-remitting multiple sclerosis; GM, gray matter, EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test, 3-sec and 2-sec trials; *$p \leq 0.002$

Correlation analysis between MRI and cognitive measures

At one-year follow-up, significant associations between cognitive measures and GM/WM regions were found. Correlation analysis among GM structures showed no relationship with processing speed or executive functions, but with memory and social cognition measures (**Table 9A**).

As for GM regions and memory tests, we found significant associations with the SPART and SPART-D, ROCF copy and delay recall. SPART immediate recall was correlated with a single cluster (x, y, z = 17, 20, -9; 297 voxels) and AVOI in the right nucleus caudatus (t = 4.59, 994 voxels, 8.5% label) and putamen (t = 3.88, 1064 voxels, 1.7% label); SPART-D with one cluster (x, y, z = 15, 9, 6; 217 voxels) in the right nucleus caudatus (t = 4.60, 994 voxels, 5% label). ROCF measures were associated with a single GM cluster: the copy (x, y, z = -5, -16, 1; 425 voxels) in the left thalamus (t = 3.58, 1100 voxels, 14.2% label); the delay recall (x, y, z = 18, 6, 16; 261 voxels) in the right nucleus caudatus (t = 4.23, 994 voxels, 11% label).

For social cognition measures, only sadness of the Emotion Attribution and Theory of Mind tasks showed a significant correlation with GM regions. In particular, sadness was related to two clusters located in both frontal lobes (right, x, y, z = 42, 5, 30; 328 voxels; left, x, y, z = -39, 20, -5; 321 voxels). The first with AVOI in the right inferior frontal operculum (t = 5.06, 1399 voxels, 6.2% label), the second in the left orbital and triangular inferior frontal gyrus (t = 4.90, 1690 voxels, 4.4% label; t = 4.61, 2529 voxels, 1.3% label) and insula (t = 4.50, 1858 voxels, 1.5% label). Theory of Mind Test revealed a borderline correlation with one cluster (x, y, z = 36, -19, -24; 212 voxels), involving the right fusiform gyrus (t = 4.21, 2518 voxels, 1.8% label) and the parahippocampal gyrus (t = 4.03, 1132 voxels, 3.5% label).

Cognitive measure	Cerebral region	Side (Right/Left)	Talairach Coordinates			Z scores
			x	y	z	
SPART	Caudate nucleus	R	17	20	-9	3.80
	Putamen	R	11	9	4	3.35
SPART-D	Caudate nucleus	R	15	9	6	3.81
ROCF copy	Thalamus	L	-5	-16	1	3.15
ROCF delay recall	Caudate nucleus	R	18	6	16	3.58
Sadness	Inferior frontal gyrus, opercular	R	42	5	30	4.07
	Inferior frontal gyrus, orbital	L	-39	20	-5	3.99
	Inferior frontal gyrus, triangular	L	-53	24	-5	3.82
	Insula	L	-51	21	4	3.75
ToM	Fusiform gyrus	R	36	-19	-24	3.57
	Parahippocampal gyrus	R	33	-27	-27	3.45

Table 9A. Correlation analysis between memory and visual measures, sadness, ToM and gray matter regions in patients with relapsing-remitting multiple sclerosis; SPART, Spatial Recall Test, immediate recall; SPART-D, Spatial Recall Test, delay recall; ROCF, Rey-Osterrieth Complex Figure; ToM, Theory of Mind Test

As for WM regions, correlation analysis revealed a significant association only with processing speed and executive measures, namely SDMT, PASAT-3 and Stroop test (**Table 9B**). SDMT was associated with two clusters, both identified by consistent outside areas. The first (x, y, z = 11, -21, -27; 3121 voxels) was in the right cerebellar lobule X (t = 4.25, 159 voxels, 8.5% label); the second (x, y, z = 41, -21, -9; 833 voxels) in the right hippocampus (t = 4.62, 946 voxels, 7.5% label). PASAT-3 was related to one cluster (x, y, z = -35, -51, -51; 168 voxels), with AVOI in the left cerebellar lobule VIII (t = 6.19, 1887 voxels, 3.6% label). Finally, the Stroop test was correlated with a single WM cluster (x, y, z = 8, -84, -0; 450 voxels), in the right lingual gyrus (t = 5.38, 2300 voxels, 5.3% label) and calcarine fissure (t = 4.11, 1861 voxels, 3.3% label).

Cognitive measure	Cerebral region	Side (Right/Left)	Talairach Coordinates			Z scores
			x	y	z	
SDMT	Cerebellum X	R	14	-36	-45	3.59
	Hippocampus	R	47	-28	-8	3.82
PASAT-3	Cerebellum VIII	L	-35	-51	-51	4.66
Stroop	Lingual gyrus	R	8	-84	-0	4.25
	Calcarine fissure	R	21	-81	-9	3.50

Table 9B. Correlation analysis between white matter regions and processing speed and executive measures in patients with relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; PASAT-3, Paced Auditory Serial Addition Test, 3-sec trial

3.4 Discussion and conclusions

The main purpose of the current MRI study was to examine the effects of MS on cognition and brain structure in a homogeneous group of patients with RRMS at the early stages of the disease and low level of disability compared to healthy subjects. Secondly, we were also interested in analyzing the main MS-related changes over time, using both morphological and neuropsychological investigations.

MRI outcomes: Atrophy of global and regional GM volumes

The first important result was the identification of a temporal atrophy pattern in the RRMS group compared to normal controls. Although there was no evidence of changes in total brain and WM volumes, a significant density reduction was demonstrated in the cortical and deep regions of GM. This atrophic pattern, which included the right inferior temporal gyrus and middle temporal gyrus-pole (i.e., covering the anatomical portion of the temporal pole near the middle temporal gyrus), was the same at the beginning and at the end of the study. At baseline, there were also reductions with a borderline significance in the left putamen and insula that disappeared in one-year follow-up. Since the second MRI measurement was performed on fewer patients, it is likely that this cluster did not reach the same significance criterion used for the baseline evaluation. Instead, a considerable atrophy in deep GM and cerebellum emerged after one year. Although the cluster was at the significance limit, the amygdala, globus pallidus and putamen were more reduced in the right hemisphere in RRMS than healthy subjects. However, no follow-up neuroimaging was available for the control group, which does not help us fully understand whether these effects, namely the shift of atrophy from the left (putamen and insula) to the right (amygdala, globus pallidus and putamen) hemisphere, were completely and directly related to the disease. Despite the limited sample size and the lack of one-year MRI control measures, current findings suggest that these deep structures of GM are somewhat more susceptible to atrophy than other cortical areas (Riccitelli et al., 2011). Considering that basal ganglia are a core feature of MS pathology in both GM/WM and are connected to cortical regions implicated in mainly affected cognitive

domains in MS (Batista et al., 2012; Bermel et al., 2002; Middleton & Strick, 2000), a reduction in these structures and in the temporal cortex and/or their connections could account for deficits noted in our patients. The pattern of atrophy we found together with correlations of cognitive measures with cortical and deep fronto-temporal regions also agreed with previous MS findings on the regional lesion volume and cerebral reduction of GM (DeLuca et al., 2015; Riccitelli et al., 2011; Rocca et al., 2015). Among these, the thalamus showed significant associations with tests of verbal memory (SRT-D), processing speed (SDMT) and visuoconstructive abilities (ROCF copy). Being a highly integrated structure with multiple cortico-subcortical connections (basal ganglia, hippocampus, amygdala, cingulate cortex, orbitofrontal cortex, and others), the thalamus plays a central role in cognitive functioning. As such, damage to thalamic structures or their network can have a negative impact on arousal, executive functions, emotional and episodic memory, spatial learning and memory. Thalamus also has extensive cortical connections with frontal brain areas, whose connectivity is hypothetically necessary to perform complex activities involving the organization and functions of praxis (e.g., ROCF task). Accordingly, the thalamus represents one of the most relevant brain regions at risk of atrophy during the initial stages of MS (Marasescu, Cerezo García & Aladro Benito, 2016).

The last cluster that emerged from volumetric comparison after one year involved a substantial part of the cerebellum (14.2%). In particular, a significant reduction in both cerebellar Crus II and in the right cerebellar Crus I was found in the RRMS group compared to controls. Several structural and functional studies have reported abnormalities in various cerebellar regions (Crus I and II; lobules VI, VII and VIII) and their anatomical connections, suggesting that the cerebellum may play a role in the variability of clinical outcomes (Loitfelder et al., 2014; Morgen et al., 2006; Sarica, Cerasa & Quattrone, 2015). Although the involvement of the cerebellum in MS has not been well defined, it was traditionally considered to be strictly related to motor dysfunctions of MS patients. In recent years, the extensive role of GM structures and the cerebellum in MS pathology has been demonstrated, already in early phases of the disease, highlighting the involvement of the posterior ‘cognitive’ cerebellum, including

the Crus I and II and lobules (Stoodley & Schmahmann, 2010). Imaging data, albeit with some discrepancies, suggest that cerebellar volume is moderately related to clinical and cognitive outcomes (Cerasa et al., 2012, 2013; Damasceno, Damasceno & Cendes, 2014; Romascano et al., 2014; Weier et al., 2014).

Neuropsychological outcomes: Memory-related dysfunctions are more prominent. Can practice effects mask the cognitive impairment?

As for the cognitive assessment in RRMS, results appear to be interesting. Taking into consideration a conservative approach in defining what constitutes MS-related cognitive impairment, namely the failure in at least two neuropsychological tests (Calabrese et al., 2009), primary results showed that more than half of the RRMS patients (52.4%) were impaired in major cognitive domains. These included verbal and visuospatial memory, speed and not speed-based executive functions, and visual abilities. In this regard, as each test evaluated multiple cognitive abilities simultaneously, the mentioned domains we used represented a convenient accommodation, for example, grouping all speed-based tasks under the same category. Specifically, patients obtained significantly worse scores than controls in the following: short- and long-term visuospatial memory, long-term verbal memory, verbal/visuospatial working memory, visuoperceptive abilities, processing speed and sustained attention, inhibition of interference, and phonemic fluency. However, these impairments in RRMS group tended to flatten over time. At six-month follow-up, long-term visuospatial/verbal memory, short-term visuospatial memory (i.e., SPART), processing speed (i.e., 2-sec PASAT), and visuoperceptive abilities appeared to have improved in patients. After one year, also phonemic fluency was no longer significantly different with respect to controls, while both verbal and visual working memory (i.e., non-speeded executive functions), processing speed and interference inhibition (i.e., Stroop test) remained significantly impaired. In addition, short-term verbal/visuospatial memory (forward digit span and Corsi block), which showed no difference from controls at the baseline or after six months, appeared to be compromised after one year. From these results, we can draw some considerations.

Firstly, repeated measure analysis on the six-month follow-up showed time effects not only for cognitive measures that were significantly improved or worsened, but also for those that were not compromised compared to healthy subjects. On the one hand, this means that a 'practice effect' had probably occurred for some tasks, although alternative forms of tests were used. For instance, tasks such as PASAT are known to be sensitive to practice effects (i.e., patients often display poorer performance when first tested due to lack of familiarity with the task) (Schoonheim et al., 2012). The effect of learning is not entirely alleviated by using parallel test modules, since it derives from short-term repetition of the assessment (Amato, Zipoli & Portaccio, 2006), as it is the case with a six-month follow-up. Alternatively, time effect was also true for those cognitive measures (i.e., SRT-LTS, SRT-CLTR, ROCF-delay recall, SDMT, 3-sec PASAT) that were not impaired in any evaluation compared to the results obtained from normal subjects. In other words, the time-related practice effect did not depend on differences with control scores, unlike the criterion used to define cognitive impairment, which means that at six months there was an actual compromise, albeit mild (23.9%). From a qualitative point of view, the use of Z scores allowed us to explain those cognitive deficits that remained stable in the face of performance fluctuations and learning effects. Longitudinal studies with long-term follow-up have also shown that cognitive deficits can remain stable or even improve over time. These impairments tend, hence, to progress but at different rates, speed and frequency, and with a great inter-subject variability (Amato et al., 2001, 2010; Schwid et al., 2007). Secondly, although learning to perform the task is a common result of longitudinal studies on MS-related cognitive deficits (Amato, Zipoli & Portaccio, 2006), in our opinion it was not possible to modify the neuropsychological protocol without failing in validity and reliability criteria. Despite the known learning effects of some tasks, such as PASAT, a report protocol that did not include an intermediate evaluation at least for cognitive tests could also produce unreliable results. Among these, there was the risk of overestimating the presence of deficits that were attributable to performance (e.g., the fear or anxiety of making mistakes) and not to a real difficulty. In this sense, PASAT itself is also known to be influenced by the emotional burden (Costa

et al., 2017), which may explain why the patients failed the performance at the baseline, but not at six-month or one-year evaluations.

At the second follow-up, which was about six months after the previous assessment, the picture had slightly changed. Deficits in visuospatial working memory (i.e., backward Corsi block) that patients showed at baseline and six-month measurements compared to controls had significantly deteriorated. Performance in Stroop task and backward digit span had slightly improved, but they remained deficient. Of note, short-term verbal/visual memory, as measured by the forward digit span/Corsi block, showed a significant decline between the beginning and the end of the study. This outcome is consistent with DeLuca et al. (2004) showing that, although slow processing speed is evident at the earliest stages of MS, there may be a threshold of brain pathology after which executive impairment emerges as an independent deficit. For this reason, the challenge faced by clinicians is to select the most appropriate battery for capturing patients' true deficits, and where executive functions are concerned, this may mean relying upon speeded and non-speeded tasks to provide dimensionality in making an assessment as accurate as possible. In this second evaluation, despite the decrease in the number of failed tests, the proportion of cognitive impairment had increased to 30.9%. According to what was discussed on the six-month follow-up, after one year the practice effect was reduced, highlighting the deficits that remained stable and those that deteriorated over time. Clearly, there was a minimal but significant impairment. This outcome was in agreement with our MRI findings, which could account for the prominent memory deficits shown by patients even after one year. Since there was no change in brain volumes between the first and second MRI measurements in RRMS group, this could also explain the reason why no other deficit had emerged. Consistent with recent literature (DeLuca et al., 2015; Riccitelli et al., 2011; Rocca et al., 2015; Sarica, Cerasa & Quattrone, 2015), poor memory performance was related to GM reduction in fronto-temporal regions (inferior frontal gyrus, middle and superior temporal cortex, thalamus, insula, nucleus caudatus, putamen) and cerebellum (Crus II, lobule VII).

Memory is more affected than processing speed: There is no relationship between cognitive impairment and other variables

Overall, memory appears to be one of the most frequently disturbed cognitive abilities. In the early stages, the deficit concerns learning strategies and involves inefficient recovery from short- and long-term memory and working memory. All these impairments can occur regardless of MS-related clinical variables and vary considerably among patients due to high-order cognitive process deficits (Grzegorski & Losy, 2017). In our cohort, the RRMS group had more difficulty in retrieving information from the short-term storage and performing executive task, especially those under restricted time conditions. Patients encountered more problems in speed-based tests, but processing speed deficits were less than memory impairments, as their performance tended to improve over time. They also showed poor visual perceptive abilities, but their mean scores did not reach pathological cut-off values and improved already at the first follow-up. Another aspect we investigated concerned the relationship between cognitive, mood and neurological measures in the RRMS group (data not shown). Considering clinical variables, we found no association between neuropsychological performance and time since diagnosis, treatment duration and physical disability. Even if this topic is still controversial, our results corroborate the hypothesis of no direct relationship between these variables (Grzegorski & Losy, 2017). As previously reported, although the progression of the disease may have an impact on cognitive performance, this effect would only be visible after a sufficiently long period of time (Amato et al., 2010). EDSS score is a global measure of neurological deterioration primarily driven by motor impairment and therefore is largely insensitive to changes occurring in cognition (Gudesblatt et al., 2016). In our study, the effects of disease progression, severity, treatment, and mood were not related to the cognitive domains investigated in any evaluation. Of note, only after one year an increased MFIS score, measuring the impact of fatigue, was significantly associated with an inferior performance on the backward Corsi block (p = 0.001), which could partly account for the slight deterioration of the visuospatial working memory ability. Another possibility, which will be discussed further below, is that the improvement of psychological symptoms over time could also have

promoted better performance in the observed measures. Although we did not find a significant relationship between depression, anxiety, psychological symptoms and cognitive abilities, an indirect impact of emotional-behavioral characteristics on our dependent measures cannot entirely be ruled out.

Role of the cerebellum on cognitive performance

Our findings about the consistency of the deficits observed in backward Corsi block and digit span and Stroop task, can also be explained in view of the relationship between structural networks and cognitive functioning. In a recent work, Yoon and colleagues (2017) were the first to link *in vivo* GM anatomical connectivity between the parietal cortex and cerebellum in humans and to further associate this structural connectivity with intelligence. In their study, authors applied a recently developed approach to extract structural networks, source-based morphometry, which is a multivariate extension of VMB to acquire common morphological features from GM concentration. In accordance with previous DTI and fMRI studies (Cole et al., 2012; Segall et al., 2012), Yoon and coworkers (2017) reported that their structural networks, i.e. frontal component and cerebello-parietal component, revealed patterns similiar to the executive control network and the default-mode network. In particular, the cerebello-parietal component, composed of the Crus II and inferior parietal lobule, showed a signficant association with both intelligence and verbal fluency, which was comparable to the link between the WM parieto-ponto-cerebellar tract and verbal intelligence (phonological storage processing and verbal encoding) observed by others (Chen & Desmond, 2005; Kamali et al., 2010; Macher et al., 2014). It is worth noting that these results are also consistent with functional studies that have investigated the more detailed anatomical features of the cerebellum. It has been demonstrated that the default-mode network, lateral temporal cortex, and inferior parietal lobule were functionally connected with Crus I and II in the cerebellar cortex, revealing the potential influence of this network on high-level cognition (Barton & Venditti, 2014; Buckner et al., 2011). From these considerations, we can assume that the cerebellum has an undoubted effect on cognitive functions, but the nature of this relationship is still unclear and further research on MS pathology is needed.

In this regard, one of the most interesting results of the current study was that a large portion of the cerebellum showed a significant volumetric reduction in the RRMS group compared to healthy subjects at one-year follow-up, involving the right Crus I and both Crus II of cerebellar hemispheres. These and other areas of the cerebellum were correlated with speed-based measures in WM. In particular, lower scores at SDMT and PASAT-3 were related to atrophy in the right X and left VIII lobules of the cerebellum, respectively. In our study, speeded and non-speeded tasks (Stroop task, phonemic fluency, backward digit span and Corsi block, and PASAT-2) were also associated with frontal-temporal regions of GM (inferior frontal gyrus, insula, thalamus, amygdala, hippocampus, Rolandic and Heschl gyrus), and with temporo-parietal-occipital areas of both GM/WM (thalamus, hippocampus, middle temporal gyrus-pole, inferior and superior temporal gyrus, supramarginal and postcentral gyrus, middle occipital lobe, lingual gyrus and calcarine fissure).

In recent years, functional neuroimaging and lesion studies have focused on the critical role of the cerebellum in cognition providing a detailed mapping of its involvement. It has been shown that there are several tight anatomical connections with a number of higher-level cortical regions, including the prefrontal cortex and the posterior parietal and occipital areas that show diffuse projections to different cerebellar regions via the thalamus and the pons (Stoodley & Schmahmann, 2010; Tedesco et al., 2011). These regions have also been shown to be related to cognitive impairment as measured by neuropsychological tests, especially those based on speed (i.e., SDMT, PASAT and verbal fluency). Unlike phonemic fluency that is a sensitive indicator of speed-based executive ability, PASAT and SDMT are primarily measures of sustained attention and auditory/visual processing speed. There is a known controversy over the use of these two tests as measures of working memory or executive functioning (Costa et al., 2017; DeLuca et al., 2004; Lengenfelder et al., 2006; Parmenter, Shucard & Shucard, 2007). Despite this, PVSAT, a visual version of PASAT, is considered a common working memory fMRI task, which is widely employed in MS populations to assess the functional integrity of the parieto-prefrontal network as well as of the cerebellum (Bonzano et al., 2009; Cerasa et al., 2012; Forn et al., 2006; Hayter, Langdon & Ramnani, 2007;

Parmenter et al., 2006; Sarica, Cerasa & Quattrone, 2015). In a series of studies, a reduced functional connectivity between the right cerebellum (Crus I and lobule VIII) and the superior parietal lobules was associated with poorer performance on speed-based measures. This impaired connectivity between the cerebellum and frontal-temporal regions, due to GM volume losses, has shown to contribute to the failure of cognitive compensation in MS people (Cerasa et al., 2012, 2013; Rocca et al., 2014; Romascano et al., 2014; Weier et al., 2014). The authors also reported that cognitively impaired patients were characterized by loss or redistribution of brain hubs in the Crus I and lingual gyrus (Rocca et al., 2014).

Interpreting our findings in light of these recent studies, the link between cerebellar abnormalities and cognitive impairment can be explained in the following ways. First, patient deficits may be due to a dysfunctional anatomical connection between the cerebellar lobules and parietal areas (Cerasa et al., 2012; Rocca et al., 2014). Not surprisingly, memory performance (i.e., SRT-D and SPART-D) were correlated with fronto-temporal regions and cerebellum, while executive (i.e., phonemic fluency, Stroop test), working memory (i.e., Corsi block-tapping task) and processing speed (i.e., SDMT) measures were associated with posterior parietal-occipital regions of both GM and WM. In one year, as the cerebellar atrophy had emerged, cognitive deficits that remained stable were related to verbal/visual working memory, interference inhibition, attention, and processing speed. While the correlation between GM regions and executive measures disappeared, a significant relationship in WM was found between speed-based (i.e., SDMT and PASAT-3) tasks and the posterior areas of cognitive cerebellum and between interference inhibition (i.e., Stroop test) performance and occipital cerebellar connections (lingual gyrus and calcarine fissure). As noted, these findings are consistent with the pattern of regional distribution of GM damage, according to which patients with RRMS have a prominent involvement of deep structures, including thalamus, insula, superior temporal gyrus, and middle occipital gyrus (Riccitelli et al., 2011). They also shed new light on the possible involvement of the posterior cerebellar and parieto-occipital areas in contributing to deficits in high-order cognitive abilities. On this point, a drawback of our study was the inability to investigate the microstructural alterations of WM, often not

visible in conventional MRI. The VBM method that we used, is based on a voxel-wise comparison of regional GM density and is less well suited to identify minimal WM changes. In fact, our comparative analysis did not show significant reductions in the volume of WM, which can be detected by more sophisticated techniques such as DTI metrics. Therefore, we observed a cerebellar volume difference in GM, but the extent to which this atrophy was driven by WM damage remains speculative. Research suggests that DTI abnormalities may even be detected in patients without any cerebellar signs, and then that microstructural alterations could represent a significant biomarker of morphological and cognitive changes occurring especially in the early stages of MS (Deppe et al., 2016).

Gender, age and processing speed as indicators of GM atrophy

Another intriguing result was that the GM volume in the RRMS group at one-year follow-up was predicted by sex, age, and SDMT score. A first regression model showed that the cognitive domain referred to as Speeded Executive Functions was a significant predictor of the GM volume of patients after one year, in addition to demographic variables. As a result, we performed further analysis to determine which of the speed-based functions within this domain was the strongest predictor. SDMT is a typical mental processing speed measure. Although no difference was found between patients and controls on this task, poor performance on SDMT was related to a significant density reduction in GM/WM regions. More interesting, performance on SDMT was indicative of the GM volume after one year, along with sex and age factors. Even though a precise localization of a cognitive domain on a specific brain region has not been clearly demonstrated, several studies on the involvement of cortical and deep GM and cerebellum showed good ability of SDMT to predict the course, diagnosis, and disability of the disease, and to correlate with MRI findings (Cerasa et al., 2013; Drake et al., 2010; Parmenter, Shucard, & Shucard, 2007; Romascano et al., 2014; Weier et al., 2014). Our results corroborate such assumption and support the use of this neuropsychological measure especially in the clinical field to detect MS-related underlying changes.

For what concerns demographic variables, there is a marked intersubjective variability in brain volume in addition to age and gender effects, all of which may mask the effects of the disease. For this reason, if the measured brain volume is not adjusted for head size, height, or weight, and controlled for age and sex, the reliability of results may decrease. Previous studies have shown that brain atrophy is associated with physiological aging and that the degree of cerebral reduction varies by gender, being more prominent in men than in women. Others have reported the opposite, suggesting that this issue is still controversial (Xu et al., 2000). Even though the presence of works in this field is relatively poor, studies on gender-related effect of genetic variables and brain atrophy on cognitive impairment in MS have confirmed a greater involvement of men than women (Chard et al., 2002; Salvettieri et al., 2004). Unlike what was expected from MRI measurement in which sex and age were used as covariates, in our regression model performed on GM volume of the RRMS group, we were interested in identifying which factors were able to predict a volumetric reduction over time. Therefore, we divided our patients into two age-based groups, noting that there was an age-related difference both at baseline and follow-up, with younger patients having a reduced GM atrophy than older ones. About the gender, the effect of this variable became significant only on one-year measurement, with women having a lower GM volume than men. We can hypothesize that this result was due to the characteristic of the RRMS sample consisting mainly of women. However, the aforementioned heterogeneity makes it difficult to correctly evaluate gender differences in brain atrophy on age-related changes, unless regional volume differences in the brain are examined in detail. This issue remains unsolved and therefore a future perspective could be to overcome these drawbacks, by clarifying the age-related gender effect on brain atrophy among different GM sub-regions.

Social cognition outcomes: Negative emotions are the most affected

With regards to social cognition and ToM measures, primary outcomes showed that RRMS group was significantly more impaired than healthy subjects in recognizing negative emotions, in particular sadness and anger. After one year, overall social cognition abilities were improved in patients, especially anger was no longer

compromised compared to normal controls. However, they still showed greater difficulty in recognizing sadness, which was significantly worse than both the normal controls and their responses at the beginning of the study. Anyway, the proportion of patients with impaired social cognition had decreased from 50% to 14.3%.

Consistent with previous literature dealing with various degrees of disease severity (Dulau et al., 2017; Gleichgerrcht, Tomashitis & Sinay, 2015; Henry et al., 2009, 2011; Kraemer et al., 2013; Ouellet et al. 2010; Patil et al., 2017; Pöttgen et al., 2013; Prochnow et al., 2011; Roca et al., 2014), our composite scores suggested that appreciation of others' minds, behaviors and emotions was faulty in MS, especially in the first evaluation. These impairments tended to level out over time, except for affective states. According to recent evidence supporting a selective impairment for negative emotions, (Banati et al., 2010; Bora et al., 2016; Cotter et al., 2016; Henry et al., 2009, 2011; Krause et al., 2009; Lenne et al., 2012; Mike et al., 2013; Phillips et al., 2011; Prochnow et al., 2011), the RRMS group initially showed a worse recognition of sadness and anger (up to a third of patients), but after one year only the sadness deficit remained substantial. The ability to attribute affective states is known to be related to the frontal lobe and to its connections with several brain structures, in particular the limbic system (Abu-Akel, 2003; Ruffman et al., 2008). Research suggests that a disconnection between the amygdala and prefrontal areas could account for the failure in recognition of sadness and anger (Adolphs, 2002; Kalbe et al., 2010; Shamay-Tsoory & Aharon-Peretz, 2007; Stone, Baron-Cohen & Knight, 1998). Among the few existing MRI studies, there is good evidence of a correlation between the recognition of affective states, in particular unpleasant emotions, and the GM volume in various subcortical structures and cortical regions: amygdala, putamen and anterior cingulum (Batista et al., 2017), temporal pole and inferior temporal gyrus (Mike et al., 2013), insula (Krause et al., 2009), fusiform gyrus (Batista et al., 2017; Mike et al., 2013), and orbitofrontal cortex (Batista et al., 2017; Krause et al., 2009). This hypothesis was supported by our MRI findings that highlighted, in addition to the right temporal cortex atrophy, a significant volumetric reduction of GM regions in patients compared to controls, involving the left insula and putamen at the baseline, and the right amygdala, putamen and globus pallidus at the follow-up. They also pointed out a significant

association between social cognition measures and GM regions: more precisely, between sadness and anterior cingulate gyrus, inferior frontal operculum, insula, orbital and triangular inferior frontal gyri; and between Theory of Mind task and fusiform gyrus and parahippocampal gyrus. These relationships can also be explained based on interesting research on functional connections of the anterior cingulate cortex with the medial parietal and temporal lobes (Metzler-Baddeley et al., 2012). The anterior cingulum is known to be involved in evaluating the salience of emotional and motivational information and in mediating the emotional activation between internal and external stimuli. In addition, the activation of a portion of the cingulum referred to as the subcallosal cingulate cortex has been found to be specifically associated with the emotion of 'sadness' (Phan et al., 2004). The insula is considered a limbic integration structure due to its multiple connections with thalamus nuclei, amygdala, orbitofrontal cortex, olfactory cortex, anterior cingulate cortex, and superior temporal sulcus. It is also an interface between physiological sensations and higher-level systems, including cognitive control, attentional processes, emotional responses, and empathy (Menon & Uddin, 2010). The anterior division of the cingulum and insula forms a 'salience network' that functions to segregate the most relevant among internal and extrapersonal stimuli to guide behavior. In this way, the salience network acts as an integral hub, whose main role is to mediate information flow across other brain networks to generate appropriate behavioral responses (Seeley et al., 2007). This functional link is relevant for understanding the relationship between brain and behavior, as it provides an interface between feelings, cognition and action, which may explain the neural basis of some affective and social cognition disorders (Menon & Uddin, 2010). In summary, we assumed that a minimal damage of this complex circuit could account for the recurrence of emotional deficits in RRMS patients, which may lead to inadequate affective and behavioral responses.

Alternatively, another possible explanation for our findings concerns the time-related effect on the performance of emotional recognition. While the other social skills remained stable over time, the signed-ranks analysis revealed that there was a significant effect only for two measures of ToM. In particular, 57.1% (n. 24) of subjects improved in the recognition of stories containing anger and 59.5% (n. 25) worsened in those describing

sadness. Considering these results, it was unlikely that a testing effect on learning had occurred. Rather, this dissociation between the two negative emotions can be explained in light of changes in the patients' global emotional state after one year. As discussed below, many symptoms of psychological distress were attenuated at the second follow-up, especially those related to anxiety and hostility, which could also clarify why a more accurate recognition and attribution of anger occurred. In contrast, new depressive symptoms emerged in patients compared to controls, not due to the effect of time but more likely due to transient changes in mood, which could be responsible for the worsening of scores in stories containing descriptions of sadness. In a nutshell, there is a close relationship between the ability to appreciate the distinction between the self and others and therefore between correctly attributing mental states to others and recognizing one's own. We believe that, on the one hand, the improvement of the psychological state has partly influenced the better performance on anger recognition tasks in patients at follow-up; on the other, that the presence of atrophy in important cortico-subcortical structures along with emerging depressive symptoms has contributed to the persistence of failures in the attribution of sadness. Finally, we also assessed the relationship of social cognition measures with fatigue, duration of the disease and treatment, and physical disability, without finding any association. Consistent with recent evidence, the ability to understand affective states did not depend on these variables, as people with MS may have difficulties in interpersonal contexts regardless of clinical features of the disease (Bora et al., 2016; Cotter et al., 2016).

Psychological features, mood and quality of life

As far as emotional-behavioral aspects are concerned, compared to healthy subjects, at the baseline MS group reported significant psychological distress, including symptoms of somatization, obsessive-compulsiveness, hostility and paranoia, and a high severity index. After one year, the self-reported emotional state of the patients was significantly better in many dimensions, although the global severity was slightly but not statistically improved. However, they now experienced depressed mood. With regard to the quality of life, the average scores indicated medium to high physical and mental health that

remained relatively stable over time. Both measures were not significantly correlated with the performance on cognitive and social tests at any time, but showed significant associations with MRI measurements (data not shown). In particular, physical health was significantly related in GM to various regions of both frontal lobes (anterior cingulum; insula; inferior, superior, orbital and medial frontal gyrus), to the right temporal cortex (middle and inferior temporal gyrus) and to many areas of both cerebellar hemispheres (Crus I and II; lobules VI, VIIB, VIII, IX; vermis VII, VIII, IX). While mental health showed significant correlations with temporo-parieto-occipital regions in the left hemisphere (hippocampus, parahippocampal gyrus, superior and inferior parietal gyrus, lingual gyrus).

One of the purposes of this study was to qualitatively explore the emotional and behavioral aspects of MS. Therefore, we observed the evolution of mood and psychological features resulting from MS diagnosis. Initially, the patients showed an excessive somatic activation, characterized in their physiological relevance and biological manifestations and related to the somatically considered anxiety. They also reported intrusive thoughts and ruminations, aspects of control and coercion both at a cognitive and at a behavioral level. Difficulties in interpersonal relationships and in coping with the obstacles of everyday activities could produce anger, intolerance, frustration, hypercriticism, and a sense of persistent injustice. In addition, the presence of particularly rigid and uncontrollable convictions, often associated with hostility, and oriented to the interpretation of signs and significant events, could result in a tendency towards the development of suspicious, critical and distrustful attitudes towards others. In this situation, the individual is isolated or disconnected from the normal network of daily relationships.

While the other psychological aspects improved over time, the depressive symptoms became more prominent after one year. Patients had negative thoughts about themselves, their behavior and their surroundings, characterized by pessimism, lack of hope, slowing down, self-criticism, loss of interests, and sometimes death ideas. At the second follow-up, a significant negative relationship also emerged between the SCL-PSY scale and three Faux Pas task subscores (p = 0.002), although neither had ever shown significant

differences with the controls. In particular, the ability to identify social *faux pas*, recognize false-beliefs and infer intentionality was significantly worse when the PSY score increased (data not shown). This subscale measures momentary fluctuations in the subject's adaptation and balance and can vary due to stressful episodes or associated disorders such as depression. In our sample, no patient had a diagnosis of major depression. Considering that mood scales (i.e., BDI and STAI-X) were never related to social and non-social performance in any evaluation, with the exception of the one-year SCL-PSY measuring temporary psychological distress (Derogatis, Lipman & Covi, 1973), at this time-point we could not know what events or circumstances had made patients more depressed or if this was just an interim variation of their mood. Furthermore, measures of quality of life (physical and mental health) were controlled for depression on MRI and did not change significantly over time, which may suggest that their mood depended on external circumstances which were not necessarily related to the disease. Considering the quality of life in a more specific way, the two main dimensions analyzed did not show a significant association with cognitive tests, in agreement with previous literature (Baumstarck-Barrau et al., 2011). However, they revealed significant correlations with the atrophy measures found in our MRI outcomes, especially with regard to the relationship between physical health and fronto-temporal and cerebellar regions. Overall, these findings suggest that the individual perception of physical health was related to disease activity based on MRI but not to cognitive impairment. Nevertheless, patients measured their quality of life with other external factors, which could still ensure a satisfying and rewarding life despite MS.

Changes in the global emotional state may affect social and cognitive performance

There was a complex relationship between the emotional aspect and subjective perception of health or illness in our patients. In particular, the RRMS sample was a homogeneous group consisting of individuals with recent diagnosis (up to 3 years) or who were starting pharmacological treatment. Some of them were still underage when the study started, so they had to reach their legal age to be recruited. Accordingly, we assessed the impact of MS diagnosis on emotional state of patients when they were still in a phase of adaptation

to the disease. This may partially explain why patients showed various psychological symptoms at the baseline evaluation, many of which disappeared after one year. It is possible that the high emotional responsiveness, due to the recent diagnosis and/or drug therapy, affected the cognitive performance, especially at the beginning of the study. On the other hand, once psychological symptoms were reduced, the patients' test performance benefited as well. Nevertheless, other external and internal factors might have come into play and influenced the emotional state of our patient cohort.

Depression, anxiety and fatigue are all multidimensional symptoms and represent the direct consequence of CNS damage caused by MS. The pathogenesis underlying these symptoms is still only partially understood; but is considered to be due to a disconnection between cortico-subcortical areas important to the limbic system. The emotional disturbances would be caused by both lesions and atrophy in the fronto-temporo-parietal tract, regardless of neurological disability. Fatigue would be the direct result of MS disease leading to both physical and mental depletion. All these aspects can reduce the efficiency of cognitive processes causing deficits in memory, executive functions, and processing speed (Bradshaw & Rose, 2008). Emotional disorders, in addition to the biological damage, are linked to internal psychological mechanisms that have affective implications. For instance, the failure to recognize and accept a chronic and degenerative illness such as MS may disturb the individual homeostasis, delaying the cognitive and emotional processing of the disease. Other psychological mechanisms that people with MS put in place at the onset of diagnosis to cope, include concerns about disease-related consequences, development of new coping and problem-solving strategies, adaptation of decision-making skills. All of these are factors that require a certain period to be processed, accepted and actuated. Consequently, the extent to which a person perceives to have a good mood, health and quality of life depends on the interplay between these multiple factors – physical, cognitive, emotional, psychological, social, and so on – all equally important and crucial to the satisfaction and well-being of any individual. Taking all these arguments into account, we observed that MS-related aspects had significant emotional and psychological consequences on our patients. As previously noted, for some individuals with MS, deficits in comprehending emotional information may contribute to

their difficulties in maintaining effective social interactions (Beatty et al., 2003; Bora et al., 2016; Cotter et al., 2016). In light of these facts, it is possible that deficits in recognizing the mental states of others, especially affective ones, are related to the perceived distress in psychological well-being and that this, in turn, influences the way in which individuals interact with people significant to them in real situations. We can assume that, on the one hand, MS patients may have learned over time new strategies to cope and live with their condition and, on the other hand, that taking charge of healthcare and pharmacological treatment of RRMS occurring at the early stages is another important aspect of the illness, which may have contributed to improve their emotional symptoms and thus their psychological adaptation to the disease.

Another possible explanation: The reserve theory

The concept of reserve, in this context, deserves a mention. The reserve model regards the ability to mediate the association between brain damage and the presence or absence of some clinical outcomes. Firstly, it suggests that clinical and functional deficits result once cerebral atrophy exceeds a certain critical threshold; but there are individual differences, such that at a given level of disease pathology, some patients show cognitive impairment, while others do not. Secondly, it assumes that the ability to optimize or maximize performance, when task difficulty is increased, is promoted through the recruitment of additional cognitive resources and differential brain networks, which reflect the use of alternative cognitive strategies (Stern, 2002, 2009). Models addressing this hypothesis have attempted to examine whether possessing more of a reserve factor (e.g., brain size before disease onset, years of education, or intellectually enriching activities) would protect an individual from cognitive decline after the onset of the disease. In particular, evidence from recent fMRI studies shows that people with MS require more brain resources than normal controls to complete working memory tasks, suggesting that these patients are more reliant on their cognitive reserve to achieve performance similar to that of healthy individuals (Sandroff, Schwartz & DeLuca, 2016). Although we were not able to directly test this hypothesis in the current study, we can presume that the observed trend towards improving performance in the RRMS group,

despite some stable deficits and cortical and deep GM atrophy, was due to a variety of aspects. These could concern both the individuals (e.g., partial effects of practice in tasks) and their disease (e.g., mild RRMS and brain atrophy on MRI). Then, there were other equally important aspects, in which it was not entirely possible to establish the relative contribution of each to another (e.g. reduction of psychological symptoms, good level of education, learning of new strategies to tackle the disease and its consequences, early and inclusive healthcare, positive perception of health-related quality of life, enriching cognitive leisure activities, meaningful interpersonal relationships, and so forth). Considering this, everything that is not directly measurable with objective tools and is part of the patients' life experience plays a key role in their adaptation and psychological well-being.

Weaknesses and strengths

The current study is not without its limitations. First of all, the sample size was sufficient to depict differences between patients and controls, but it was too small for any further secondary analysis. Secondly, the tools we used for the cognitive assessment might have had some flaws, like the potential practice effects, or the fact that they were originally designed for neurological populations with more severe cognitive impairment. As MS is a multifocal disease, in which there is no direct relationship between individual WM/GM pathways and a specific cognitive ability, its clinical manifestations are relatively heterogeneous. In addition, our patients had a very mild and early RRMS, in which multiple compensation mechanisms were actuated. Validated measures, for the MS evaluation designed to detect subtle differences over time, are needed to counteract the practice effect of many cognitive tests. Furthermore, although we took the precaution of carrying out the cognitive assessments in two sessions of about an hour each, the administration of many such tests and questionnaires could have generated a fatigue effect, and this may have led to more compromised performance than expected in the RRMS group. Overcoming these neuropsychological gaps would allow a more accurate and clinically meaningful assessment of important aspects of cognition and behavior in the MS population. Another limitation was the lack of follow-up control data for both

cognitive and MRI samples, due to logistical drawbacks, that could have helped to clarify the nature of deficits and their neural substrates in the RRMS group. In addition, MRI investigation was performed with a conventional univariate approach that did not allow to detect minimal volume changes or abnormalities of WM, considered equally important to our outcomes. Lastly, we recruited patients with mild RRMS, thus limiting possible generalization of our results. Nevertheless, this choice reflected the larger outpatient population usually attending MS centers.

In spite of these limitations, we believe that our study has helped to clarify many aspects of cognition related to MS pathology. First, we conducted a careful investigation of several neuropsychological and psychological features, including emotion processing abilities and aspects of quality of life, together with the observation of brain morphological changes. Initially, the RRMS group revealed a wide range of deficits, including memory, processing speed, executive functions, working memory, visual abilities, and negative emotions. The consistency of these impairments changed over time, so that patients were more prone to dysfunctions related to memory and recognition of sadness. All these impairments were not significantly correlated with other clinical factors, such as the duration or severity of the disease, but their potential effects should not be entirely excluded. Many MS-related aspects were also associated with the emotional and psychological consequences of the disease, which might affect the mood and well-being of these patients. We do not propose this as an original conclusion, but we have endeavored to extend the body of research in terms of generality and specificity through a wide and comprehensive assessment rarely found in previous studies. Secondly, there was a typical pattern of temporal atrophy in RRMS patients that may account for their prominent memory deficits. Volumetric reduction involved both cortical and deep GM structures. Sex, age, and SDMT scores were able to predict GM atrophy at one-year follow-up, proving that SDMT is a sensitive neuropsychological tool in evaluating MS-related changes. We have also shown that cerebellar volume alterations may play a key role in MS pathology, leading to significant impairment in memory, processing speed and executive abilities. Although its function is not entirely clear, emerging studies confirm the importance of the connections between the cerebellum and parietal areas on high-

order cognitive processes. Finally, cognitive performance of RRMS patients has led to some unexpected and interesting results. The impairments in this group tended to flatten over time. This result is important for two reasons. First, we have demonstrated that there is a minimal but significant cognitive impairment. Second, a considerable room for improvement in the early MS is possible. Of course, some practice effects were anticipated due to the close time-points between the measurements, but at the same time, there is a threshold of cerebral tolerance which must be trespassed before cognitive disturbances achieve clinical relevance (Stern, 2002). In other words, it is possible that patients improved because they had partly learned to perform cognitive tasks and because they partly had a mild RRMS in which the cognitive reserve and compensatory mechanisms were still in place. Nevertheless, MS brain pathology had effects on their cognition, emotions and behaviors, some of which were not subject to improvement.

Conclusions

In closing, our findings corroborate the hypothesis that cognitive impairment occurs in early MS, but its effect is mild to the point that a number of people with MS cannot be distinguished from healthy subjects on many neuropsychological tests. Since cognitive disturbances might reflect neuroinflammation as well as degenerative processes, which prevent the identification of a single clinical profile of the disease, further studies need to consider these cumulative effects. Besides, only an early management of healthcare occurring at the initial stage of the disease may contribute to the well-being and quality of life of people with MS.

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Me, my family, my friends, my fiancé

APPENDIX

SUBJECT CASE REPORT FORM

- CLINICAL DATA –

FUNCTIONAL AND MORPHOLOGICAL CORRELATES OF COGNITIVE AND SOCIAL COGNITION IMPAIRMENT IN MULTIPLE SCLEROSIS

A LONGITUDINAL STUDY

Subject Number __ __ - __ __ __

Subject Initials __ - __ - __

Enrollment date __ __ - __ __ __ - __ __ (Day-Mon-Yr)

NPS Evaluation □ T0 □ T1 □ T2

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Data di nascita ____/____ /____ Età _____ Scolarità _____

Indirizzo _____ Telefono _____

Professione _____ EDSS _____ Dominanza manuale ☐ Dx ☐ Sx

Esordio SM _____ Terapia farmacologica in atto_____

Anamnesi

_____

_____

_____

_____

TEST COGNITIVI E AFFETTIVO-COMPORTAMENTALI

BRB – NT	Punteggio grezzo	Punteggio Corretto	Cut-off
SRT – LTS			23.3
SRT – CLTR			15.5
SPART			12.7
SDMT			37.9
PASAT 3			28.4
PASAT 2			17.1
SRT – D			4.9
SPART – D			3.6

BDI	Punt. _____		Cut-off ≤ 9
STAI – X1	Punt. _____	Perc. _____	Cut-off ≤ 90
STAI – X2	Punt. _____	Perc. _____	Cut-off ≤ 90
MFIS	Punt. _____		Cut-off < 38
MSQoL	P. Salute Fisica _____		P. Salute Mentale _____
SCL-90	Somatiz_____	Depres_____	AnsiaFobica_____
Index_____	OC_____	Ansia_____	Psicoticismo_____
	SensInterp_____	Ostilità_____	IdeaParan_____

	Punteggio grezzo	Punteggio corretto	PE
Span di Cifre diretto			
Span di Cifre inverso			
Corsi Span diretto			
Corsi Span inverso			
Memoria di prosa			
Copia figura di Rey			
Figura di Rey-recall			
Fluenza fonemica			
Fluenza semantica			
Test di Street			
Test di Stroop			
FAB			
WCST - Punteggio globale - Errori perseverativi - Errori non perseverativi - Fallimenti nel mantenere il set - Categorie completate		 — —	 —

Faux Pas	/ 10	NoFauxPas	/ 10
Controllo FauxPas	/ 10	Controllo NoFauxPas	/ 10
Totale domande	/ 40		

Test di Attribuzione delle Emozioni:

	min-max	Punt.		min-max	Punt.
(T)	5-10	/ 10	(F)	10-10	/ 10
(P)	7-10	/ 10	(R)	5-10	/ 10
(IMB)	5-12	/ 12	(INV)	0-3	/ 3
(DIS)	1-3	/ 3			

Test delle Situazioni Sociali:	min-max	Punt.
N comportamenti normativi (A)	12-15	/ 15
N violazioni corrette identificate	21-25	/ 25
Gravità violazioni	24-68	/ 75

Test di Teoria della Mente	11-13	Tot	/ 13

BRB–NT / Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis

Protocollo

Stesura curata da:

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Nome:_____ Data test:_____

Età:_____ Scolarità:_____ Sesso: M F

	Punteggio grezzo	Punteggio corretto	Cut-off
SRT-LTS Selective Reminding Test, Long Term Storage	_____/72	_____	23.3
SRT-CLTR Selective Reminding Test, Consistent Long Term Retrieval	_____/72	_____	15.5
SPART 10/36 Spatial Recall Test	_____/30	_____	12.7
SDMT Symbol Digit Modalities Test	_____/110	_____	37.9
PASAT 3 Paced Auditory Serial Addition Test	_____/60	_____	28.4
PASAT 2 Paced Auditory Serial Addition Test	_____/60	_____	17.1
SRT-D Delayed Recall of the Selective Reminding Test	_____/12	_____	4.9
SPART-D Delayed Recall of the 10/36 Spatial Recall Test	_____/10	_____	3.6

SRT - Selective Reminding Test

*Somministrazione. Dire al soggetto: "*Questo è un test di memoria. Tra poco le leggerò un elenco di 12 parole. Quando avrò terminato, le chiederò di ripetere quante più parole ricorderà, senza seguire alcun ordine particolare. Successivamente le dirò le parole che non ha ricordato e le chiederò di nuovo di ripetere tutte le parole dell'elenco, comprese quelle che mi aveva già detto".

Leggere la lista al ritmo di una parola ogni due secondi. Al termine, chiedere al soggetto di ripetere tutte le parole che ricorda. Terminata la rievocazione, dire al soggetto: *"Queste sono le parole che lei non ha detto".* Quindi rileggere solo le parole che non sono state rievocate, sempre al ritmo di una parola ogni due secondi. Al termine della rilettura, dire: *"Ora cerchi di ripetere tutte le parole, comprese quelle che mi ha già detto"*. Seguire la stessa procedura per le successive ripetizioni, ovvero rileggere sempre e solo le parole non ripetute nella prova appena conclusa.

Se tutte le parole sono ricordate correttamente per due volte consecutive, il test viene interrotto e al soggetto viene assegnato il punteggio massimo.

Parole	1	2	3	4	5	6
Burro						
Braccio						
Costa						
Lettera						
Regina						
Cabina						
Pollo						
Biglietto						
Erba						
Motore						
Follia						
Sforzo						

	1	2	3	4	5	6	Totale
SRT-LTS							_____/72
SRT-CLTR							_____/72

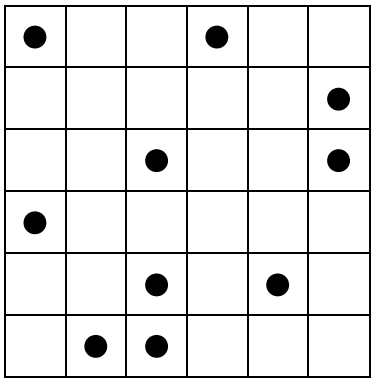
SPART - 10/36 Spatial Recall Test

Somministrazione. Posizionare la tavola vuota davanti al soggetto ed i 10 gettoni di lato alla tavola. Quindi dire: *"Questo è un test di memoria visiva. Tra un istante le mostrerò una scacchiera uguale a quella che ha di fronte, tranne per il fatto che vi saranno disegnati dei gettoni neri. Le farò vedere la scacchiera per 10 secondi e poi la toglierò. Quindi le chiederò di posizionare i gettoni nella scacchiera che ha di fronte, così come erano in quella che le ho mostrato"*. Mostrare quindi la scacchiera per 10 secondi e, subito dopo, chiedere al soggetto di riprodurla. Tutti i gettoni dovranno essere posizionati nella scacchiera.

La prova viene ripetuta per 3 volte consecutive con identica modalità.

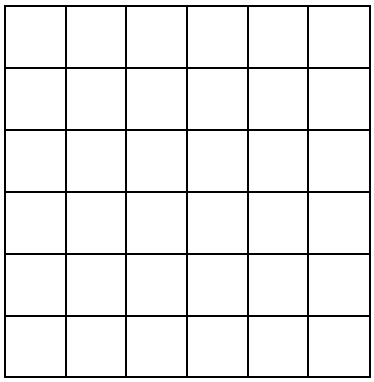
In caso di difficoltà nella manipolazione dei gettoni da parte del soggetto, questi potrà indicare la loro posizione sulla scacchiera e sarà l'esaminatore a collocarli nelle caselle segnalate.

Soggetto



Esaminatore

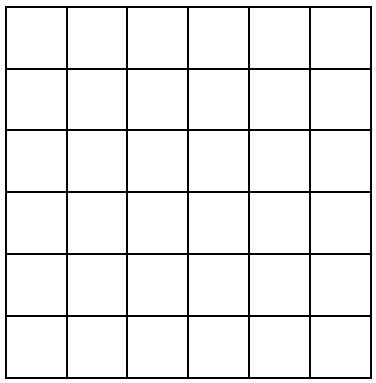
1° prova



Posizioni corrette

Posizioni errate

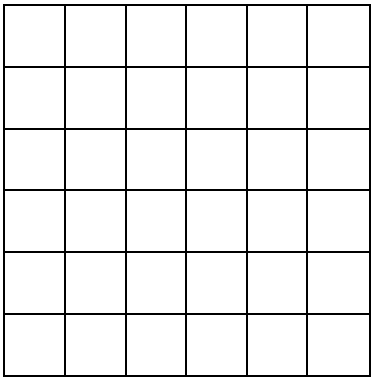
2° prova



Posizioni corrette

Posizioni errate

3° prova



Posizioni corrette

Posizioni errate

SDMT - Symbol Digit Modalities Test

Somministrazione. Dire al soggetto: *"Osservi questi riquadri (indicare la legenda). Come può vedere ogni riquadro è diviso in due parti: in quella superiore c'è un segno, in quella inferiore un numero. Ciascun segno è abbinato ad un numero. Ora osservi qui sotto: come può vedere nel riquadro superiore c'è un segno, mentre il riquadro inferiore è vuoto. Vorrei che lei mi dicesse quale numero deve essere messo in ciascuno dei seguenti riquadri*". Fare un esempio con i primi due items, quindi dire: *"Ora, quando le dirò INIZI lei mi dica, il più rapidamente possibile, i numeri da mettere nei singoli riquadri fino alla doppia linea*". Dare il via, registrare le risposte degli items d'esempio e correggere il soggetto in caso di errore.

Quando gli items d'esempio sono correttamente completati, dire:"Iniziando dalla doppia linea, mi dica quale numero deve essere messo in ciascun riquadro, per quanti più riquadri può senza saltarne nessuno. Se vuole può tenere il segno con il dito. Quando termina una riga passi subito alla successiva. Lavori il più velocemente possibile, senza fare errori fino a quando la fermerò"*.*

Dare inizio al test e concedere al soggetto 90 secondi.


5
9 3 4 9 1 2 4 6 9 2 4 9 2 9 4
20
6 2 9 4 3 2 1 6 9 4 2 8 6 1 7
35
6 3 5 7 9 1 5 6 7 3 4 8 1 6 5
50
4 6 3 9 2 6 9 3 2 5 8 7 1 2 6
65
8 3 7 1 2 5 6 3 4 1 5 8 4 7 9
80
2 8 5 4 1 2 6 8 9 5 4 3 2 7 6
95
4 7 5 8 1 5 7 3 9 8 4 9 6 1 2
110
3 4 9 2 6 4 9 2 8 5 1 3 6 7 8

PASAT 3 - Paced Auditory Serial Addition Test

Somministrazione. L'esaminatore dice: "*Fra poco le farò ascoltare una voce registrata che pronuncerà una serie di numeri ad una sola cifra, enunciati a distanza di 3 secondi l'uno dall'altro. Ascolti i primi due numeri, li sommi e mi dica il risultato. Quando sentirà il numero seguente, lo sommi a quello che è stato detto immediatamente prima. Continui a sommare l'ultimo numero al penultimo. Non mi deve dire la somma complessiva, ma solo la somma degli ultimi due numeri che ha sentito. Ad esempio se sente i numeri 5, 7, 3, 2 lei deve dirmi 12, 10 e 5".* Se può essere d'aiuto si può fare un esempio scritto e ripetere le istruzioni fino a che il soggetto non le ha comprese appieno. Aggiungere: *"E' un compito difficile. Se le capitasse di perdere il ritmo riprenda a sommare da quel punto. Adesso le faccio ascoltare una breve lista, in modo che possa fare pratica".* Avviare quindi la traccia di esempio (*Pasat 3_esempio*) e far esercitare il soggetto fino a che non la esegue correttamente. Passare quindi alla traccia del test (*Pasat 3_test*).

1 4 8 1 5 1 3 7 2 6 9
5 ___ 12___9 ___ 6 ___ 6 ___ 4 ___ 10___9 ___ 8 ___ 15 ___

4 7 3 5 3 6 8 2 5 1
13___11___10___8 ___ 8 ___ 9 ___ 14___10___7 ___ 6 ___

5 4 6 3 8 1 7 4 9 3
6 ___ 9 ___ 10___9 ___ 11___9 ___ 8 ___ 11___13___12 ___

7 2 6 9 5 2 4 8 3 1
10___9 ___ 8 ___ 15___14___7 ___ 6 ___ 12___11___4 ___

8 5 7 1 8 2 4 9 7 9
9 ___ 13___12___8 ___ 9 ___ 10___6 ___ 13___16___16 ___

3 1 5 7 4 8 1 3 8 2
12___4 ____6____12___11___12___9____4 ____11___10 ___

Totale risp. corrette

PASAT 2 - Paced Auditory Serial Addition Test

Terminata la prima prova, dire: *"Questo test prevede anche una seconda parte, identica alla prima, ad eccezione del fatto che i numeri vengono pronunciati un pò più velocemente, uno ogni 2 secondi. Anche in questo caso le faccio fare pratica con una serie d'esempio"*. Avviare quindi la traccia di esempio (*Pasat 2_esempio*) e far esercitare il soggetto fino a che non la esegue correttamente. Passare quindi alla traccia del test (*Pasat 2_test*).

4 3 7 2 5 1 8 6 9 1 7
7 ___ 10___9 ___ 7 ___ 6 ___ 9 ___ 14___15___10___8 ___

9 4 6 3 5 8 1 6 2 7
16___13___10 9 ___ 8 ___ 13___9 ___ 7 ___ 8 ___ 9 ___

5 9 4 5 2 6 4 8 3 5
12___14___13___9 ___ 7 ___ 8 ___ 10___12___11___8 ___

9 7 4 2 8 5 2 1 6 4
14___16___11___6 ___ 10___13___7 ___ 3 ___ 7 ___ 10 ___

7 3 5 9 6 4 5 3 9 4
11___10___8 ___ 14___15___10___9 ___ 8 ___ 12___13 ___

1 8 3 1 6 8 5 4 2 6
5___9 ____11____4____7 ____14___13___9 ____6____8 ____

Totale risp. corrette

SRT-D – Delayed Recall of Selective Reminding Test

Dire al soggetto: "Ora cerchi di ricordare le 12 parole dell'elenco sul quale abbiamo lavorato più volte all'inizio del test"*.*

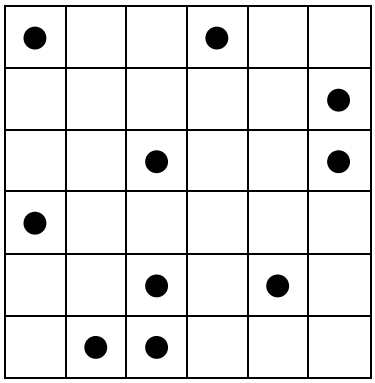
Parole	Richiamo
Burro	
Braccio	
Costa	
Lettera	
Regina	
Cabina	
Pollo	
Biglietto	
Erba	
Motore	
Follia	
Sforzo	

Totale

SPART-D - 10/36 Spatial Recall Test

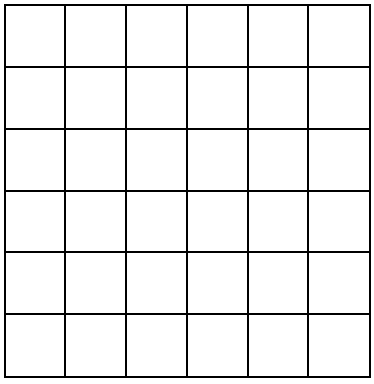
Consegnare nuovamente al soggetto la scacchiera vuota e i 10 gettoni e dire: *"Vorrei chiederle di riposizionare i gettoni come nella scacchiera che le ho mostrato in precedenza"*.

Soggetto



Esaminatore

Rievocazione differita



Posizioni corrette

Posizioni errate

TEST DI SPAN DI CIFRE

(Monaco et al., 2013)

Digit span Forward

2)	2 4	6 1
3)	5 8 2	6 9 4
4)	6 4 3 9	7 2 8 6
5)	4 2 7 3 1	7 5 8 3 6
6)	6 1 9 4 7 3	3 9 2 4 8 7
7)	5 9 1 7 4 2 8	4 1 7 9 3 8 6
8)	5 8 1 9 2 6 4 7	3 8 2 9 5 1 7 4
9)	2 7 5 8 6 2 5 8 4	7 1 3 9 4 2 5 6 8

Digit Span Backward

2)	6 1	3 8
3)	6 2 9	4 1 5
4)	3 2 7 9	1 9 6 8
5)	1 5 2 8 6	6 1 8 4 3
6)	5 3 9 4 1 8	7 2 4 8 5 6
7)	8 1 2 9 3 6 5	4 7 3 9 1 2 8
8)	9 4 3 7 6 2 5 6	7 2 8 1 9 6 5 2

Tabella di correzione

Digit span forward

Età / Scol.	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*
3	-0.09	-0.04	0.01	0.07	0.13	0.19	0.26	0.34
5	-0.23	-0.18	-0.13	-0.07	-0.01	0.05	0.12	0.20
8	-0.39	-0.35	-0.29	-0.24	-0.18	-0.11	-0.04	0.04
13	-0.61	-0.56	-0.51	-0.45	-0.39	-0.32	-0.25	-0.17
17	*	-0.70	-0.65	-0.59	-0.53	-0.47	-0.47	-0.32

PG PC PE

Digit span backward

Età / Scol.	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*
3	0.14	0.19	0.24	0.29	0.35	0.41	0.48	0.55
5	-0.06	-0.02	0.03	0.08	0.14	0.20	0.27	0.35
8	-0.31	-0.26	-0.21	-0.16	-0.10	-0.04	0.02	0.10
13	-0.62	-0.58	-0.53	-0.48	-0.42	-0.36	-0.29	-0.21
17	*	-0.79	-0.74	-0.69	-0.63	-0.57	-0.50	-0.42

PG PC PE

PE	0	1	2	3	4
Digit span forward	< 4.26	< 4.60	< 5.29	< 5.75	> 5.75
Digit span backward	< 2.65	< 3.29	< 3.79	< 4.33	> 4.33

CORSI SPAN FORWARD

(Monaco et al., 2013)

(2)	5-6	**(3)**	4-7-2
	4-7		8-1-5
	9-5		3-6-1
	5-7		4-1-5
	4-9		9-5-8
(4)	9-3-1-5	**(5)**	8-5-4-1-9
	6-5-4-8		2-3-5-4-1
	4-9-8-7		3-4-1-7-2
	1-6-5-3		7-9-3-4-1
	6-2-3-7		8-1-9-2-6
(6)	5-3-2-4-6-7	**(7)**	5-9-1-7-4-2-8
	9-8-1-4-6-5		4-1-7-9-3-8-6
	2-3-1-5-9-4		5-8-1-9-3-8-6
	2-4-6-3-5-1		3-8-2-9-5-1-7
	2-3-6-4-9-5		6-1-9-4-7-3-8
(8)	1-7-6-4-8-3-2-5	**(9)**	2-6-5-7-9-3-4-8-1
	5-8-3-2-6-7-1-9		8-2-3-4-1-7-9-6-5
	7-1-2-3-4-6-8-5		3-4-6-7-5-8-9-2-1
	9-4-7-3-1-8-2-5		8-6-7-3-4-9-5-2-1
	7-6-9-1-2-3-8-4		4-3-1-8-7-5-6-2-9

PG	PC	PE

Tabella di correzione

Corsi span forward

Età Scol.	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*
3	0.00	0.05	0.10	0.16	0.22	0.28	0.35	0.43
5	-0.16	-0.11	-0.06	-0.01	0.05	0.11	0.18	0.26
8	-0.35	-0.31	-0.26	-0.20	-0.14	-0.08	-0.01	0.07
13	-0.61	-0.56	-0.51	-0.46	-0.40	-0.33	-0.26	-0.19
17	*	-0.73	-0.68	-0.63	-0.57	-0.50	-0.43	-0.36

CORSI SPAN BACKWARD

(Monaco et al., 2013)

(2)	5-6	**(3)**	4-7-2
	4-7		8-1-5
	9-5		3-6-1
	5-7		4-1-5
	4-9		9-5-8
(4)	9-3-1-5	**(5)**	8-5-4-1-9
	6-5-4-8		2-3-5-4-1
	4-9-8-7		3-4-1-7-2
	1-6-5-3		7-9-3-4-1
	6-2-3-7		8-1-9-2-6
(6)	5-3-2-4-6-7	**(7)**	5-9-1-7-4-2-8
	9-8-1-4-6-5		4-1-7-9-3-8-6
	2-3-1-5-9-4		5-8-1-9-3-8-6
	2-4-6-3-5-1		3-8-2-9-5-1-7
	2-3-6-4-9-5		6-1-9-4-7-3-8
(8)	1-7-6-4-8-3-2-5	**(9)**	2-6-5-7-9-3-4-8-1
	5-8-3-2-6-7-1-9		8-2-3-4-1-7-9-6-5
	7-1-2-3-4-6-8-5		3-4-6-7-5-8-9-2-1
	9-4-7-3-1-8-2-5		8-6-7-3-4-9-5-2-1
	7-6-9-1-2-3-8-4		4-3-1-8-7-5-6-2-9

PG	PC	PE

Tabella di correzione

Corsi span backward

Età	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*
	-0.83	-0.76	-0.69	-0.61	-0.52	-0.43	-0.33	-0.21

PE	0	1	2	3	4
Corsi span forward	< 3.46	< 4.29	< 4.80	< 5.37	> 5.37
Corsi span backward	< 3.08	< 3.37	< 3.99	< 4.55	> 4.55

BREVE RACCONTO

(G.Novelli, C.Papagno, E.Capitani, M.Laiacona, S.F.Cappa, G.Vallar, 1986)

Anna / Pesenti / di Bergamo / che lavora / come donna delle pulizie / in una ditta / di costruzioni / riferì / al maresciallo / dei Carabinieri / che la sera / precedente / mentre rincasava / era stata aggredita / e derubata / di 150 euro. / La poveretta / aveva 4 / bambini / piccoli / che non mangiavano / da 2 / giorni / e doveva pagare / l'affitto. / I militari / commossi / fecero una colletta.

Rievocazione immediata.....
.....
.....
.....

Rievocazione differita.....
.....
.....
.....

I Riev.	II Riev.	P.tot (I+II)/2	P. corr.	P. E.
		/28	/28	

Tabella di correzione

Scolar.	Età / Sex.	*25*	*35*	*45*	*55*	*65*	*75*
3	m	6,0*	0	0	.25	.5	.5
	f	4,0	.25	.25	.5	.5	.75
5	m	-.25	0	0	.25	.25	.5
	f	0	0	.25	.25	.5	.75
8	m	-.5	-.25	-.25	0	.25	.25
	f	-.25	0	0	.25	.25	.5
13	m	-.75	-.5	-.5	-.25	0	0
	f	-.5	-.25	-.25	0	0	.25
17	m	-.75	-.75	-.5	-.5	-.25	-.25
	f	-.75	-.5	-.5	-.25	-.25	0

Punteggi Equivalenti:

0 = da 0 a 7.50
1 = da 8 a 10
2 = da 10.50 a 12
3 = da 12.50 a 14
4 = da 14.50 oltre

STREET'S COMPLETION TEST

(Street, 1931; Spinnler e Tognoni, 1987)

A	**B**
1. fox terrier	8. cucina elettrica
2. bebè	9. aereo
3. uccello	10. cavaliere
4. corridore	11. caldarrostaio
5. soldato cinese	12. biroccio
6. automobile	13. dalmata
7. tennista	14. scimmia

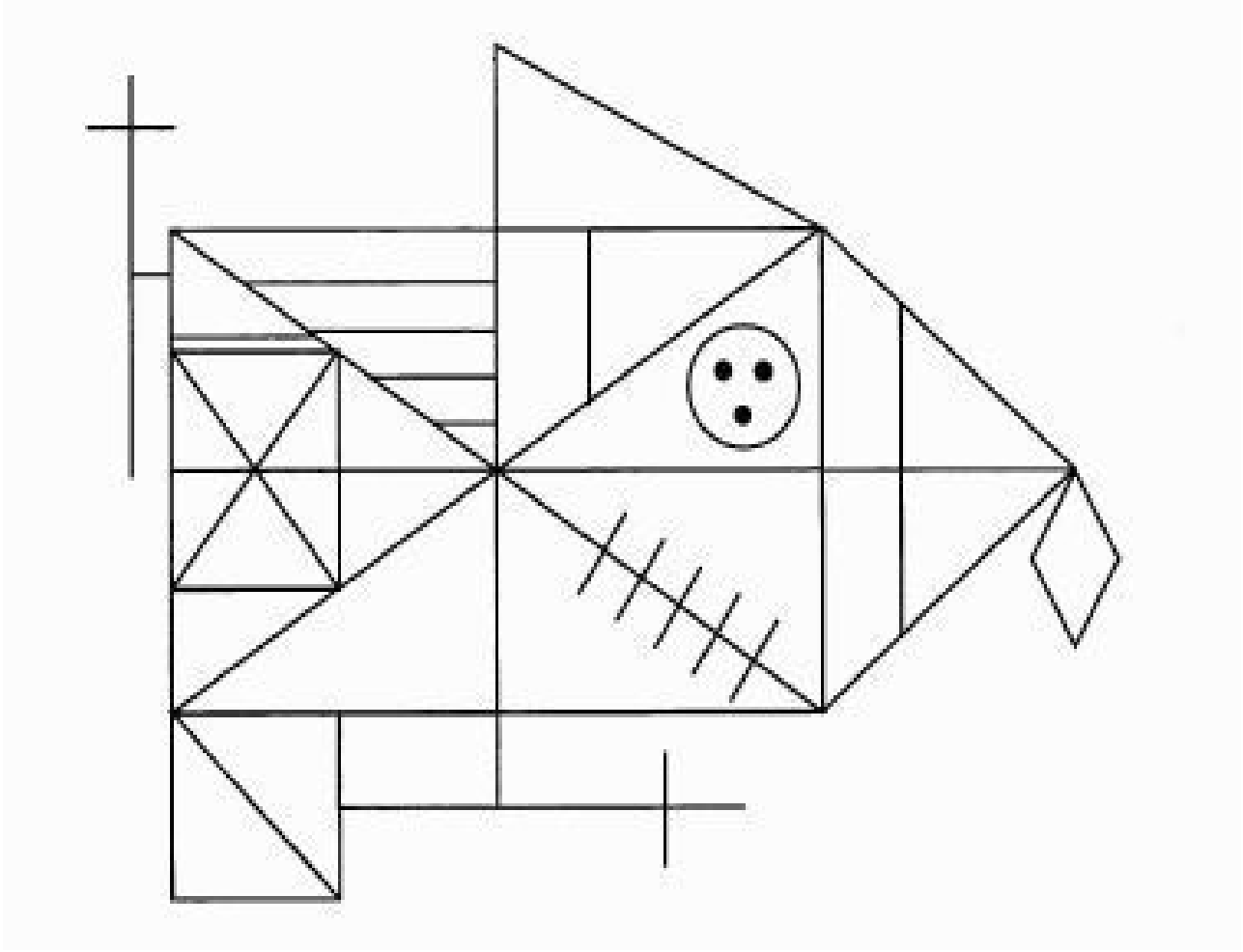
Tabella di correzione

Età Scolarità	*40*	*50*	*55*	*60*
3	-1.00	-0.25	+0.25	+0.75
5	-1.50	-0.75	-0.25	0
8	-2.00	-1.25	-1.00	-0.50
13	-3.00	-2.25	-1.75	-1.50
17	-3.50	-2.75	-2.25	-2.00

Punteggi Equivalenti:

0 = da 0 a 2.00
1 = da 2.25 a 3.75
2 = da 4.00 a 5.25
3 = da 5.50 a 7.00
4 = da 7.25 oltre

Punteggio grezzo.....
Punteggio corretto.....
Punteggio equivalente.....



TEST DI FLUENZA VERBALE PER LETTERE

(Novelli, Papagno, Capitani, Laiacona, Vallar e Cappa, 1986)

F **P** **L**

_____

Tabella di conversione

EtàScolarità	*25*	*35*	*45*	*55*	*65*	*75*
3	+7	+8	+9*	+10*	+12*	+13*
5	+4	+5	+6	+7	+8	+9*
8	- 1	+1	+2	+3	+4	+5
13	- 6	- 5	- 4	- 3	- 1	0
17	-10	- 9	- 7	- 6	- 5	- 4

*Applicabilità discutibile

Punteggi Equivalenti

0 = da 0 a 16
1 = da 17 a 22
2 = da 23 a 26
3 = da 27 a 31
4 = da 32 oltre

PUNTEGGIO GREZZO = _____
PUNTEGGIO CORRETTO = _____
PUNTEGGIO EQUIVALENTE = _____

TEST DI FLUENZA SEMANTICA

(Novelli, Papagno, Capitani, Laiacona, Vallar e Cappa, 1986)

FRUTTI **ANIMALI** **MARCHE AUTO**

Tabella di correzione

EtàScolarità	25	35	45	55	65	75
3	6	7	9	10	12	14
5	2	3	4	6	8	10
8	-2	-1	1	2	4	6
13	-6	-5	-3	-2	0	2
17	-8	-7	-6	-4	-2	0

Punteggi Equivalenti

0 = da 0 a 24

1 = da 25 a 29

2 = da 30 a 34

3 = da 35 a 38

4 = da 39 oltre

PUNTEGGIO GREZZO = _____

PUNTEGGIO CORRETTO = _____

PUNTEGGIO EQUIVALENTE = _____

STROOP TEST (Barbarotto et al., 1998)

STROOP TAV. 1 - LETTURA **W1**

	1	2	3	4	5	6	7	8	9	10
1	verde	viola	marrone	blu	rosso	blu	marrone	viola	verde	rosso
2	viola	rosso	verde	marrone	blu	verde	viola	blu	rosso	marrone
3	rosso	blu	viola	verde	marrone	viola	rosso	marrone	blu	verde
4	blu	marrone	rosso	viola	verde	marrone	verde	rosso	viola	blu
5	marrone	verde	blu	rosso	viola	rosso	blu	verde	marrone	viola
6	rosso	viola	marrone	viola	blu	marrone	verde	rosso	blu	verde
7	blu	rosso	verde	rosso	marrone	verde	viola	blu	marrone	viola
8	marrone	blu	rosso	marrone	verde	viola	rosso	verde	viola	blu
9	viola	verde	blu	verde	rosso	blu	marrone	viola	rosso	marrone
10	verde	marrone	viola	blu	viola	rosso	blu	marrone	verde	rosso

STROOP TAV. 2 - COLORI **C1**

	1	2	3	4	5	6	7	8	9	10
1	verde	rosso	blu	viola	marrone	rosso	viola	blu	verde	marrone
2	rosso	marrone	verde	blu	viola	blu	rosso	marrone	viola	verde
3	blu	verde	viola	marrone	rosso	verde	marrone	viola	blu	rosso
4	marrone	viola	rosso	verde	blu	viola	verde	rosso	marrone	blu
5	viola	blu	marrone	rosso	verde	marrone	blu	verde	rosso	viola
6	blu	marrone	viola	verde	rosso	blu	rosso	viola	marrone	verde
7	viola	rosso	marrone	blu	verde	rosso	viola	verde	blu	marrone
8	rosso	blu	verde	marrone	viola	marrone	blu	rosso	verde	viola
9	verde	viola	blu	rosso	marrone	verde	marrone	blu	viola	rosso
10	marrone	verde	rosso	viola	blu	viola	verde	marrone	rosso	blu

STROOP TAV. 3 - INTERFERENZA **CWT1**

	1	2	3	4	5	6	7	8	9	10
1	verde	rosso	blu	marrone	viola	rosso	blu	viola	verde	marrone
2	viola	blu	marrone	verde	rosso	verde	viola	marrone	blu	rosso
3	blu	verde	viola	rosso	marrone	blu	marrone	rosso	viola	verde
4	rosso	marrone	verde	viola	blu	viola	rosso	verde	marrone	blu
5	marrone	viola	rosso	blu	verde	marrone	verde	blu	rosso	viola
6	blu	marrone	viola	verde	rosso	blu	rosso	viola	marrone	verde
7	viola	rosso	marrone	blu	verde	rosso	viola	verde	blu	marrone
8	rosso	blu	verde	marrone	viola	marrone	blu	rosso	verde	viola
9	verde	viola	blu	rosso	marrone	verde	marrone	blu	viola	rosso
10	marrone	verde	rosso	viola	blu	viola	verde	marrone	rosso	blu

Risposte corrette in 30 secondi: **W1=** **C1=** **CWT1=**

Frontal Assessment Battery (FAB)

Dubouis et al.(2000), valori normativi italiani di Isella et al. (2002) e Consoli et al. (2002).

Prova	Istruzioni	Punteggio
Similarità (astrazione)	"Mi dica in cosa sono simili: - una banana e una arancia - un tavolo e una sedia - un tulipano, una rosa e una margherita"	3 risposte corrette: 3 2 risposte corrette: 2 1 risposta corretta: 1 0 risposte corrette: 0
Fluenza verbale (flessibilità mentale)	"Dica il maggior numero di parole inizianti con la lettera S, tranne nomi di persona o di città". Tempo max: 60 sec.	> 9 parole: 3 6-9 parole: 2 3-5 parole: 1 < 3 parole: 0
Go-No go (controllo e inibizione)	"Quando io batto il dito sul tavolo una volta, anche lei lo deve battere una volta" Verificare la comprensione battendo per tre volte un colpo. "Quando io batto il dito due volte, lei non deve battere" Verificare la comprensione battendo per tre volte due colpi. "Bene, risponda solo al colpo unico" Sequenza dell'esaminatore : 1-1-2-1-2-2-2-1-1-2	0 errori: 3 1-2 errori: 2 >2 errori: 1 4 errori consecutivi: 0
Sequenze motorie (programmazione)	"Guardi attentamente ciò che sto per fare". L'esaminatore esegue sul tavolo per tre volte con la mano sinistra la sequenza di Luria pugno-taglio-palmo. "Ora lei deve eseguire questa sequenza con la mano destra, prima assieme a me e poi da solo". L'esaminatore esegue lae sequenza tre volte assieme al paziente, quindi dice: "Adesso continui da solo".	6 serie consecutive da solo: 3 3-5 serie consecutive da solo: 2 3 serie consecutive con l'E: 1 0 serie consecutive con l'E 0
Ordini conflittuali (sensibilità all'interferenza)	"Quando io batto il dito sul tavolo una volta, lei lo deve battere due volte" Verificare la comprensione battendo per tre volte un solo colpo sul tavolo. "Quando io batto il dito due volte, lei lo deve battere una volta" Verificare la comprensione battendo per tre volte due colpi. "Bene, faccia sempre il contrario di ciò che faccio io" Sequenza dell'esaminatore : 1-1-2-1-2-2-2-1-1-2	0 errori: 3 1-2 errori: 2 > 2 errori: 1 4 errori consecutivi: 0
Prensione (indipendenza ambientale)	Esaminatore seduto di fronte al paziente: questi appoggia le mani sulle sue ginocchia, tenendo il palmo rivolto verso l'alto. L'esaminatore porta le mani vicino a quelle del paziente, toccando il palmo di entrambe. Se il paziente afferra le mani dell'esaminatore si ripete la prova dicendo "Da ora non prenda le mie mani".	paziente non afferra: 3 esita e chiede cosa fare: 2 afferra senza esitazione: 1 afferra in caso di divieto: 0

Punteggio_____/18 P corretto_____ PE _____

Wisconsin Card Sorting Test (WCST)

M. Laiacona, M.G. Inzaghi, A. De Tanti, E. Capitani, 2000. Wisconsin card sorting test: a new global score, with Italian norms, and its relationship with the Weigl sorting test. Neurol Sci (2000) 21:279-291

Somministrazione. Disporre le quattro carte stimolo sul tavolo, da sinistra verso destra rispetto al paziente, in questo ordine: triangolo, stelle, croci, cerchi. Quindi dire al soggetto: «*questo test è un po' strano, poiché non mi è consentito dirle molto su come farlo. Le chiederò di associare ciascuna delle carte di questi due mazzi (*indicando i due mazzi di 64 carte) *a una di queste quattro carte di riferimento. Lei deve sempre prendere la prima carta in cima al mazzo e metterla sotto la carta di riferimento a cui lei pensa che corrisponda. Non le posso dire come associare le carte, ma ogni volta le dirò se ha fatto giusto o sbagliato. Se ha sbagliato, lasci la carta dove l'aveva messa, e cerchi di mettere la carta successiva nel posto corretto. Usi il primo mazzo e poi continui con il secondo. Non c'è un limite di tempo per questo test.*

L'esaminatore deve rispondere «*giusto*» ogni volta che il soggetto associa le carte per colore e «*sbagliato*» ogni volta che il colore non corrisponde. Si procede finché il soggetto non risponde al colore per 10 carte consecutive. A questo punto l'esaminatore, senza fare alcun commento o dare alcuna indicazione, cambia criterio e valuta corrette solo le risposte alla forma. Dopo altre 10 carte posizionate correttamente dal soggetto, il criterio cambia nuovamente e vengono accettati gli accoppiamenti corrispondenti per numero, sempre senza esprimere alcun commento. Dopo altre 10 risposte corrette il criterio torna ad essere il colore e poi ancora la forma ed infine il numero, sempre con la stessa modalità e senza dare alcuna indicazione al soggetto (sequenza completa: C, F, N, C, F, N).

Il test si interrompe con l'esaurimento delle 128 carte o quando il soggetto ha completato le sei categorie previste (con 10 risposte corrette consecutive per ciascuna).

	PG	PC	PE
Punteggio Globale			
Errori Perseverativi			
Errori non Perseverativi			
Fallimenti nel mantenere il set		--	
Categorie completate		--	--

C - F - N - C - F - N

___1 C F N A	___33 C F N A	___65 C F N A	___97 C F N A
___2 C F N A	___34 C F N A	___66 C F N A	___98 C F N A
___3 C F N A	___35 C F N A	___67 C F N A	___99 C F N A
___4 C F N A	___36 C F N A	___68 C F N A	___100 C F N A
___5 C F N A	___37 C F N A	___69 C F N A	___101 C F N A
___6 C F N A	___38 C F N A	___70 C F N A	___102 C F N A
___7 C F N A	___39 C F N A	___71 C F N A	___103 C F N A
___8 C F N A	___40 C F N A	___72 C F N A	___104 C F N A
___9 C F N A	___41 C F N A	___73 C F N A	___105 C F N A
___10 C F N A	___42 C F N A	___74 C F N A	___106 C F N A
___11 C F N A	___43 C F N A	___75 C F N A	___107 C F N A
___12 C F N A	___44 C F N A	___76 C F N A	___108 C F N A
___13 C F N A	___45 C F N A	___77 C F N A	___109 C F N A
___14 C F N A	___46 C F N A	___78 C F N A	___110 C F N A
___15 C F N A	___47 C F N A	___79 C F N A	___111 C F N A
___16 C F N A	___48 C F N A	___80 C F N A	___112 C F N A
___17 C F N A	___49 C F N A	___81 C F N A	___113 C F N A
___18 C F N A	___50 C F N A	___82 C F N A	___114 C F N A
___19 C F N A	___51 C F N A	___83 C F N A	___115 C F N A
___20 C F N A	___52 C F N A	___84 C F N A	___116 C F N A
___21 C F N A	___53 C F N A	___85 C F N A	___117 C F N A
___22 C F N A	___54 C F N A	___86 C F N A	___118 C F N A
___23 C F N A	___55 C F N A	___87 C F N A	___119 C F N A
___24 C F N A	___56 C F N A	___88 C F N A	___120 C F N A
___25 C F N A	___57 C F N A	___89 C F N A	___121 C F N A
___26 C F N A	___58 C F N A	___90 C F N A	___122 C F N A
___27 C F N A	___59 C F N A	___91 C F N A	___123 C F N A
___28 C F N A	___60 C F N A	___92 C F N A	___124 C F N A
___29 C F N A	___61 C F N A	___93 C F N A	___125 C F N A
___30 C F N A	___62 C F N A	___94 C F N A	___126 C F N A
___31 C F N A	___63 C F N A	___95 C F N A	___127 C F N A
___32 C F N A	___64 C F N A	___96 C F N A	___128 C F N A

Faux Pas Test

(Stone *et al*., 1998)

1. Vittoria era ad una festa dal suo amico Franco. Stava parlando con Franco quando si avvicinò loro una vicina di casa di Franco. Questa donna disse “Salve”, poi si girò verso Vittoria e disse “Penso che non ci siamo mai incontrate prima. Mi chiamo Maria, e tu?”. “Io Vittoria”. “Qualcuno vuole qualcosa da bere?” chiese Franco.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

Se SI, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Franco sapeva che Maria e Vittoria non si conoscevano?

Come pensa che si sia sentita Vittoria?

Domanda di controllo: Nella storia, dov’era Vittoria?

Maria e Vittoria si conoscevano?

2. Il marito di Elena stava organizzando una festa a sorpresa per il compleanno della moglie. Aveva invitato Sara, un’amica di Elena, dicendole “Non dirlo a nessuno, soprattutto ad Elena”. Il giorno prima della festa Elena era da Sara, e Sara rovesciò alcune gocce di caffè su un vestito nuovo che era appoggiato su una sedia. “Oh! Avevo intenzione di metterlo per la tua festa!” disse Sara. “Quale festa?” disse Elena. “Dai, vediamo se riusciamo a togliere la macchia” disse Sara.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Sara si ricordava che la festa era una festa a sorpresa?

Come pensa che Elena si sia sentita?

Domanda di controllo: Nella storia, per chi era la festa a sorpresa?

Cosa è stato rovesciato sul vestito?

3. Gianni stava comprando una camicia che stesse bene con il suo completo. Il commesso gli mostrò molte camicie. Gianni le esaminò con cura e ne trovò una del colore giusto. Ma quando la provò nel camerino, si accorse che non gli entrava. “Temo che sia piccola” disse al commesso. “Non si preoccupi” rispose il commesso “la settimana prossima ne avremo alcune della misura più grande”. “Bene. Tornerò allora” disse Gianni.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Quando Gianni ha provato la camicia,sapeva che non l’avevano della sua taglia?

Come pensa che si sia sentito Gianni?

Domanda di controllo: Nella storia, cosa stava comprando Gianni?

Perché tornerà la settimana dopo?

4. Giulia aveva appena traslocato nel suo nuovo appartamento. Andò a far compere e acquistò tende nuove per la camera da letto. Appena finì di decorare l’appartamento, la sua migliore amica andò a trovarla. Giulia le fece fare un giro dell’appartamento e le chiese “Ti piace la mia camera da letto?”. “Quelle tende sono orribili,” disse Lisa. “Spero che ne comprerai presto delle nuove!”

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Lisa sapeva chi aveva comprato le tende?

Come pensa che Giulia si sia sentita?

Domanda di controllo: Nella storia, cosa aveva appena comprato Giulia?

Da quanto tempo Giulia viveva in quest’appartamento?

5. Roberto andò dal barbiere a farsi tagliare i capelli. “Come vuole che glieli tagli?” chiese il barbiere. “Mi piace lo stesso taglio che ho adesso, soltanto un po’ più corto” rispose Roberto. Il barbiere però tagliò i capelli davanti in modo un po’ irregolare, così dovette tagliarli più corti per regolarizzarli. “Temo che siano un po’ più corti di quanto lei abbia chiesto” disse il barbiere. “Va bene lo stesso. Cresceranno!” disse Roberto.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Mentre gli stavano tagliando i capelli, Roberto sapeva che il barbiere glieli stava tagliando troppo corti?

Come pensa si sia sentito Roberto?

Domanda di controllo: Nella storia, Roberto come voleva che gli tagliassero i capelli?

Come glieli ha tagliati il barbiere?

6. Giovanni si fermò dal benzinaio lungo la strada di casa per fare il pieno di benzina. Diede la sua carta di credito alla cassiera che cercò di usarla. “Mi scusi, la sua carta sembra smagnetizzata” disse la cassiera. “Hmmm, è strano” disse Giovanni “vorrà dire che pagherò in contanti”. Diede alla cassiera 40 Euro e disse “Vorrei il pieno di benzina verde senza piombo”.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Come pensa che si sia sentito Giovanni?

Domanda di controllo: Nella storia, cosa si era fermato a comprare Giovanni?

Perché ha pagato in contanti?

7. Sandra è una bimba di 3 anni con la faccia tonda ed i capelli biondi corti. Era a casa di sua zia Carola. Il campanello suonò e zia Carola andò a rispondere. Era Maria, una vicina. “Ciao. Hai fatto bene a fermarti” disse zia Carola. Maria disse “Salve” poi guardò Sandra e disse “Oh, non penso di conoscere questo bambino. Come ti chiami?”.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, dov'era Sandra?

Come pensa che Sandra si sia sentita?

8. Giovanna portò il suo cane Fufi al parco. Lanciò un bastoncino perché Fufi lo inseguisse. Erano lì da un po', quando passò Pamela, una sua vicina. Pamela chiese “State andando verso casa? Facciamo un pezzo di strada insieme?”. “Certo” disse Giovanna. Ella chiamò Fufi, ma era indaffarato ad inseguire dei piccioni e non arrivò. “Sembra che non sia ancora pronto per andare” disse Giovanna. “Ok! Ti vedrò più tardi” rispose Pamela.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, Giovanna dove aveva portato Fufi?

9. Nella scuola elementare Leopardi, tutte le quinte parteciparono ad una gara di poesia. Cristina ha sempre voluto diventare una poetessa da grande, così lavorò moltissimo sulla sua poesia per una settimana, poi la consegnò. Alcuni giorni dopo furono resi noti i risultati della gara: la poesia di Cristina non aveva vinto nulla, mentre un suo compagno di classe, Giacomo, aveva vinto il primo premio. Il giorno dopo Cristina era seduta in banco con Giacomo e stavano guardando il trofeo del primo premio. Giacomo disse "E' stato facile vincere in questo contesto. Tutte le altre poesie della gara erano terribili!". "Dove metterai il tuo trofeo?" chiese Cristina.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che cosa avrebbe voluto diventare Cristina da grande?

Come pensa che Cristina si sia sentita?

10. Ugo era in biblioteca. Trovò il libro sulle escursioni alle Dolomiti che stava cercando, e andò al banco per chiederlo in prestito. "Mi dispiace. Mi sembra di aver lasciato a casa il tesserino della biblioteca" disse alla bibliotecaria. "Non importa" lei rispose. "Mi lasci il nome, e se il suo nome è nel computer, può prendere il libro mostrandomi soltanto la carta di identità".

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, quale libro Ugo aveva trovato in biblioteca?

11. Giulio Rossi, il presidente di una grossa industria, organizzò una riunione per tutti i dirigenti più anziani. “Ho qualcosa da dirvi” disse. “Giovanni Moroni, uno dei vicepresidenti è molto malato, ha un tumore ed è ricoverato in ospedale”. Tutti fecero silenzio ascoltando la brutta notizia, mentre Roberto, uno della direzione, entrò in ritardo. “Ehi, volete sapere l’ultima battuta che ho imparato ieri sera? E’ la storia di quello che dice il malato terminale al medico”. Giulio Rossi disse “Beh, andiamo avanti a lavorare”.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che cosa ha detto Giulio Rossi alla riunione?

Come pensa che si siano sentite le persone alla riunione? Come pensa che si sia sentito Roberto dopo, quando ha saputo cosa era accaduto alla riunione?

12. Michele, un bambino di 9 anni, ha appena cominciato una scuola nuova. Era in uno dei bagni della scuola. Ugo e Pietro, altri due bambini, entrarono nei bagni e stavano parlando in piedi vicino ai lavandini. Ugo disse “Conosci il nuovo ragazzo della classe? Si chiama Michele. Non ti sembra strano? E poi è così basso!”. Michele uscì dal bagno, Ugo e Pietro lo videro. Pietro disse “Oh, ciao Michele! Stai andando a giocare a pallone?”.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, dov’era Michele mentre Ugo e Pietro stavano parlando?

Come pensa che si sia sentito Michele?

13. Ugo, il cugino di Carla, era venuto a farle visita. Carla preparò una torta di mele appositamente per lui. Dopo cena, lei disse “Ho preparato una torta apposta per te. E’ in cucina”. “Mmmm” rispose Ugo “ha un buon profumo! Adoro le torte, naturalmente tranne quelle di mele”.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che tipo di torta aveva preparato Carla?

Come pensa che si sia sentita Carla?

14. Carlotta comprò per la sua amica Anna un vaso di cristallo come regalo di nozze. Anna fece un grande matrimonio e le arrivarono molti regali. Dopo un anno circa, un sera Carlotta, mentre era a cena da Anna, fece cadere accidentalmente una bottiglia di vino sul vaso di cristallo, ed il vaso si ruppe. “Sono molto dispiaciuta, ho rotto il vaso di cristallo” disse Carlotta. “Non ti preoccupare. Non mi è mai piaciuto. Qualcuno me lo ha regalato per il matrimonio” rispose Anna.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI’, chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che cosa regalò Carlotta ad Anna per il suo matrimonio?

Come pensa che si sia sentita Carlotta?

15. Giovanna fu la prima attrice nel teatrino scolastico dell'anno scorso, ed all'inizio di questo anno avrebbe voluto moltissimo mantenere il ruolo di protagonista. Prese lezioni di recitazione, ed in primavera ebbe l'audizione teatrale. Il giorno che furono affisse le decisioni, andò prima della lezione per controllare la lista degli attori. Giovanna non ebbe il ruolo da protagonista, ed invece fu ingaggiata con un ruolo minore. Corse verso il suo ragazzo nel salone d'ingresso e gli raccontò cos'era successo. "Mi dispiace. Devi essere molto scoraggiata" disse il suo ragazzo. "Sì. Devo decidere se accettare o meno questa parte" rispose Giovanna.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, quale ruolo ha ricevuto Giovanna?

16. Tommaso era al ristorante. Fece cadere accidentalmente alcune gocce di vino sul vestito. "Le porto subito lo smacchiatore" disse il cameriere. Il cameriere però non era più ricomparso. Tommaso si alzò verso Gianluca, un altro cliente del ristorante, che stava in piedi vicino alla cassa aspettando di pagare, e disse "Ho fatto cadere alcune gocce di vino sul vestito. Può portarmi qualcosa per pulirmi?".

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, perché Gianluca era in piedi vicino alla cassa?

Come pensa che si sia sentito Gianluca?

17. Eleonora, una donna di 65 anni, stava aspettando il bus alla fermata. Il bus, però, era in ritardo e lei si stancò molto poiché dovette restare in piedi a lungo. Quando finalmente il bus arrivò, era pieno e non c'erano posti liberi per sedersi. Vide sul bus un suo vicino, Pietro. "Salve Eleonora. Ha aspettato a lungo?" disse il vicino. "Circa venti minuti" rispose. Un uomo giovane che era seduto si alzò e disse "Signora, vuole sedersi al mio posto?".

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, perché Eleonora ha aspettato il bus per 20 minuti?

18. Roberto aveva appena cominciato a lavorare in un nuovo ufficio. Un giorno, in corridoio, stava parlando con un nuovo collega, Andrea. "Cosa fa tua moglie?" chiese Andrea. "E' avvocato" rispose Roberto. Alcuni minuti più tardi Chiara passò di lì e sembrava molto irritata. "Ho appena avuto la peggiore telefonata della mia vita" disse loro. "Gli avvocati sono tutti così arroganti ed avidi. Non li posso tollerare". "Vuoi venire a guardare queste carte?" chiese Andrea a Chiara. "Non adesso. Ho bisogno di un caffè" replicò Chiara.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che cosa fa nella vita la moglie di Roberto per vivere?

Come pensa che si sia sentito Roberto?

19. Riccardo comprò una macchina nuova, una BMW rossa. Alcune settimane dopo, andò ad urtare contro la macchina del suo vicino, una vecchia Volvo ammaccata. La sua auto nuova non fu danneggiata per niente, né egli danneggiò molto nemmeno la macchina del vicino, fatta eccezione per un piccolo graffio nella vernice. Comunque, Riccardo bussò alla porta del vicino. Quando il vicino rispose, Riccardo disse "Mi dispiace molto, ho appena fatto un piccolo graffio sulla sua macchina". Il vicino la guardò e disse "Non si preoccupi, non è niente di grave".

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, che cosa fece Riccardo alla macchina del suo vicino?

20. Luisa andò dal macellaio per comprare della carne. Il negozio era molto affollato e rumoroso. Lei chiese al macellaio "Ha dei polli ruspanti?". Il macellaio annuì e cominciò a incartarle un pollo arrostito. Allora Luisa lo interruppe, dicendo "Non devo essermi spiegata bene. Le ho chiesto se ha dei polli ruspanti". "Oh, mi scusi" disse il macellaio "Non ne abbiamo".

Qualcuno ha detto qualcosa che non avrebbe dovuto dire?

(Tempo di reazione)

Se SI', chiedere: Chi ha detto qualcosa che non avrebbe dovuto dire?

Perché non avrebbe dovuto dire ciò?

Perché pensa che abbia detto ciò?

Domanda di controllo: Nella storia, dove andò Luisa?

Cognizione Sociale e Comportamento

(Prior, Sartori & Marchi, 2003)

TEST DELLE SITUAZIONI SOCIALI

Nelle seguenti storie alcune parti sono in carattere *italico*. Subito dopo ci sono delle parentesi. Giudichi il comportamento presentato nella parte in italico come se ne fosse testimone. Usi questa scala:

Comportamento normale in quella situazione **(A)**

Comportamento un po' strano in quella situazione **(B)**

Comportamento abbastanza strano in quella situazione **(C)**

Comportamento estremamente strano in quella situazione **(D**)

Non ci sono risposte giuste o sbagliate; quello che è importante è la sua opinione.

1) Carlo era un impiegato che lavorava in un ufficio della sua città. A mezzogiorno egli pranzava in un piccolo parco. *Spesso egli rompeva parte di un panino in piccoli pezzi, spargendoli nel terreno per i piccioni.* ( ) Un giorno, mentre si sedeva nella panchina, un passeggino venne parcheggiato proprio lì davanti. Carlo notò che vicino una giovane donna stava dondolando un bambino un po' più grande. Il bambino nel passeggino cominciò a piangere ma la mamma non lo sentiva Carlo ha imparato che quando il suo piccolo nipote grida, talvolta significa che il suo pannolino si è aperto. *Piuttosto che disturbare la madre nel parco, Carlo velocemente controllò i vestitini del bambino per vedere se poteva sentire il pannolino aperto.* ( )

2) Emilia si svegliò in ritardo il giorno del suo viaggio in aereo. C'era appena il tempo per vestirsi e andare all'aeroporto, *così saltò la sua colazione.* ( ) A mezzogiorno la hostess venne con il pranzo, ma Emilia era così affamata che una porzione non l'aveva soddisfatta. Guardò una ragazzina attraverso il corridoio che giocherellava con il suo cibo, lamentandosi: "Non riesco a mangiarlo". Emilia si sporse dal corridoio e disse: "*Se la sua piccola bambina non vuole il suo vassoio, lo può passare di qua per me?*". ( )

3) Ruggero viveva da solo e un giorno venne invitato a cena a casa di un'amica della madre. In genere egli era solito avvertire la cameriera che non mangiava carne e che avrebbe desiderato che la sua verdura gli venisse servita scondita. Quando Ruggero arrivò all'appuntamento si ricordò che non aveva toccato cibo da due ore. *Senza perdere alcun tempo, ancor prima di essere presentato, egli chiese alla cameriera quando la cena sarebbe stata servita.* ( ) Lei rispose che ci

sarebbe voluta ancora un'ora prima che il cibo fosse pronto*. Sentendo ciò, Ruggero aprì la sua valigetta, prese una mela e alcune noci e prontamente le mangiò.* ( ) Proprio prima di cena, la cameriera gli fece vedere un attraente piatto di frutti e verdure, chiedendo se gli sembrava abbastanza. "*Va bene, grazie" – disse Ruggero –* "*ma se non le dispiace io aspetterei un'altra ora per mangiare. Ho già preso qualcosa un'ora fa."* ( ).

4) Elisabetta era diabetica da tutta la vita. I dottori le avevano detto di stare molto attenta alla sua dieta per evitare serie complicazioni. Quando veniva invitata da qualcuno per un pranzo, lei spiegava il problema in anticipo*. Ma durante gli incontri importanti godeva delle conversazioni e della compagnia che trovava, aspettando di tornare a casa per mangiare.* ( )

5) Franco faceva il giardiniere. Di solito si portava il pranzo al sacco*. A mezzogiorno, Franco si lavava sempre le mani sotto un rubinetto e sedeva in una parte ombreggiata del giardino per mangiare*. ( ) Un giorno cominciò a piovere a mezzogiorno. Franco bussò alla porta della casa dove lavorava e chiese il permesso di mangiare dentro. La signora gli disse di entrare e lui individuò da solo la sala da pranzo. *Tolse le briciole dal tavolo e guardò intorno alla casa in cerca di un posto dove riposarsi*. ( ) *Il tappeto del salotto era sottile, perciò egli decise di rannicchiarsi per il suo pisolino sopra una larga poltrona*. ( )

6) Il supermercato dove Roberto era solito fare la spesa aveva una piccola scritta nella porta che diceva "E' proibito entrare scalzi in questo magazzino". Un giorno d'estate Roberto vide una bella ragazza entrare nel magazzino a piedi scalzi Roberto decise di far in modo che i piedi di lei non venissero visti dal direttore. *Spinse il suo carrello vicino e davanti a lei corridoio dopo corridoio*. ( )

7) Matteo è stato appena nominato in un importante nuovo lavoro. Alle 6 in punto del giorno in cui pensava di cominciare il nuovo lavoro, Matteo ricevette una telefonata da sua madre che stava molto male. *Matteo era molto preoccupato e così infilò un maglione sopra il suo pigiama e guidò verso la casa di sua madre per curarla.* ( ) Dopo che il dottore fu arrivato, non c'era abbastanza tempo perché Matteo ritornasse a casa sua e si cambiasse di abito*. Egli decise di andare al lavoro con il suo pigiama perché non voleva arrivare tardi al suo nuovo lavoro.* ( )

8) Giovanna si recò con sua figlia di tre anni all'aeroporto. C'erano file molto lunghe di persone che aspettavano di registrare i loro bagagli. *Giovanna si mise in coda alla fila con sua figlia.* ( ) Dopo un po' di minuti Giovanna vide sua figlia correre attraverso le uscite al controllo del passaporto. Giovanna era molto preoccupata così chiese ad una signora davanti a lei nella fila se poteva passare avanti perché aveva fretta*. La signora non rispose a Giovanna e così lei spinse la signora fuori dalla fila e per terra.* ( )

9) Era una calda giornata d'estate e Giovanni amava consumare il suo pranzo nel parco lì vicino. *Era stato parecchio caldo in ufficio così quando Giovanni arrivò nel parco si levò tutti i vestiti e mangiò il suo panino nudo.* ( )

10) Maria portò dei fiori nella casa della sua migliore amica perché la sua cara madre era appena defunta. *Ogni persona alla casa era molto turbata e così per tentare di tirarli su di corda Maria decise di raccontare una barzelletta.* ( )

11) Un giocatore di baseball arrivò tardi ad una partita cruciale e si rese conto di aver dimenticato la sua divisa a casa. *Egli non aveva tempo per ritornare a casa e prenderla, così entro nello stadio con la sua biancheria intima.* ( )

12) Arturo, un uomo vecchio e fragile, un giorno si recò alla stazione metropolitana. C'era molta gente nel metrò e non riuscì a trovare un posto a sedere*. Subito dopo una giovane ragazza lo vide e gli offrì il suo posto*. ( ) Egli notò che la ragazza stava mangiando una tavoletta di cioccolata. Lui era molto affamato visto che non aveva potuto mangiare quel giorno. *Si girò verso la ragazza e le chiese se le avrebbe dato un po' della sua cioccolata.* ( )

13) William stava bevendo in un pub con dei suoi amici*.* Quando si incamminò fuori dal pub, un uomo picchiettò forte sulla sua spalla. *William gli diede un pugno in bocca.* ( )

14) Susanna stava facendo la spesa. Stava comprando delle caramelle per sua figlia Katia. Mentre stava uscendo dal negozio, un uomo la afferrò e tentò di prenderle la borsa. *Susanna gli diede uno schiaffo in faccia*. ( ) L'uomo corse via lungo la strada*. Katia, la figlia di Susanna, cominciò a piangere.* ( )

15) Francesco ha dei vicini di casa molto ricchi. Essi comprano sempre nuove cose per la loro casa: nuovi frigoriferi, nuovi televisori. Ogni volta che comprano qualcosa di nuovo, essi gettano via quella vecchia*. Un giorno i vicini di Francesco comprano un nuovo impianto musicale*. ( )

16) Elisabetta, una segretaria, un giorno era al lavoro e stava battendo sul suo computer. Poi, l'altra segretaria, Luisa, entrò nella stanza, posò la sua borsa per terra attaccata alla sedia di Elisabetta e poi se ne andò*. Elisabetta non aveva soldi e così aprì la borsa e tirò fuori 50.000 £ dal portafoglio.* ( )

17) Bruno non vedeva un suo amico da un paio di settimane. ( ) Lo rincorse lungo la strada per prenderlo. *Bruno salutò il suo amico.* ( ) Bruno e il suo amico chiacchierarono per almeno dieci minuti. Poi decisero di prendere un caffè in un bar lì vicino. Quando arrivarono, l'amico di Bruno disse: "Sono appena ritornato da Roma". *Bruno pensa che ciò sia molto divertente e comincia a ridere*. ( )

18) Roberto è completamente esausto e vorrebbe andare disperatamente a dormire. Ma deve vedere il suo capo a casa sua sta sera. Prende la metropolitana verso la casa del suo capo. La camminata verso la casa dell'uomo lo rende ancora più stanco. Il suo capo lo accoglie e lo invita dentro e gli dice che tornerà giù tra pochi minuti, visto che deve sistemare delle cose di sopra. Roberto va nella stanza principale della casa. C'è un tappeto piuttosto spesso. Si sente ancora tanto esausto. *Così Roberto si stende sul grosso tappeto e decide di fare un sonnellino.* ( )

19) Maria si è velocemente addormentata a letto. E' andata a letto nuda. Alle tre in punto del pomeriggio si sveglia. In casa c'è qualcuno con lei. L'intruso deve essere un ladro. *Maria salta giù e corre fuori di casa e lungo la strada senza niente addosso*. ( )

20) Riccardo è andato al cinema. La maschera gli ha mostrato il suo posto a sedere ed egli è pronto per vedere il suo film. Poi, cinque minuti più tardi, la maschera ritorna con alcune altre persone. A Riccardo è stato assegnato il posto sbagliato. Egli avrebbe dovuto essere nella fila dietro. *Riccardo è furioso e urla alla maschera per cinque minuti.* ( )

21) Roberta è una persona molto timida e paurosa. Un giorno lei e la sua migliore amica vanno in un bar. L'amica di Roberta le racconta una barzelletta che le era stata detta il giorno prima. *Roberta pensa che la barzelletta sia molto divertente e ride.* ( ) Si siedono a un tavolo e continuano a chiacchierare. L'amica di Roberta le racconta un incubo che ha avuto la notte prima. *Roberta è terrorizzata e si nasconde sotto il tavolo*. ( )

22) Luca prende l'ascensore al suo lavoro. E' un freddo gelido. Fuori c'è neve spessa ma al suo lavoro non si accenderà il riscaldamento. L'ascensore è affollato. La persona accanto a Luca nell'ascensore indossa un grosso maglione di pelo. *Luca è così freddo che si spinge contro quella persona tentando di scaldarsi*. ( )

23) Marco si trova nella vasca da bagno a casa sua. *E'sdraiato lì da quindici minuti e adesso sta leggendo un libro.* ( ) Improvvisamente suona il campanello della porta. Marco sa che potrebbe essere il postino che quella sera avrebbe dovuto consegnare un pacchetto per lui. E' cruciale che Marco riceva il pacchetto quella sera. Marco corre fuori dal bagno e cerca un asciugamano ma non riesce a vedere né asciugamani né vestiti. *Marco corre alla porta e la apre nudo.* ( )

24) Giada è nel suo ufficio. Il giorno prima aveva comprato un nuovo paio di scarpe che sono troppo strette e le comprimono i piedi. Battendo al suo computer, Giada non riesce a sopportare a lungo il dolore e così si toglie le scarpe e i calzini e si massaggia i piedi. Un'ora più tardi il capo di Giada la chiama nel suo ufficio. L'incontro sarà lungo perché devono discutere parecchie cose. Di nuovo, Giada sente un forte male ai piedi. *Giada si toglie le scarpe e i calzini e si massaggia i piedi.* ( )

25) La madre di Franco è appena morta. L'intera famiglia è al funerale*. La sorella di Franco comincia a piangere.* ( ) Il sacerdote invita al silenzio per un minuto di rispetto. Improvvisamente e accidentalmente, l'uomo dietro Franco si muove e dà un calcio molto forte a Franco nella tibia. Franco viene colto di sorpresa. Salta e lancia un guaito. La sorella di Franco ha visto tutto. *Lei pensa che ciò sia molto divertente e comincia a ridere*. ( )

TEST DI TEORIA DELLA MENTE

Quelle che seguono sono brevissime storie con dei protagonisti. Risponda alle domande provando a mettersi dal punto di vista del personaggio citato.

1)Katia ed Emma sono due bambine che stanno giocando a casa. Emma prende una banana dal cestino della frutta e l'avvicina all'orecchio. Dice a Katia:" Guarda! Questa banana è un telefono!"

E' vero quello che Emma ha detto?

Perché Emma ha detto questo?

2)Giuseppe voleva comprare un gattino, così andò a trovare la signora Rossi che possedeva molti gattini che non poteva tenere. In realtà la signora Rossi amava i gattini e non voleva che nessuno facesse loro del male, nonostante non potesse tenerli tutti lei. Giuseppe non era sicuro di volere uno dei gattini della signora Rossi. Ma la signora Rossi disse: "Se nessuno compra i gattini sarò costretta ad affogarli!"

E' vero quello che ha detto la signora Rossi?

Perché la signora Rossi ha detto questo a Giuseppe?

3)Gianni andò a casa di Chiara per la prima volta. Gianni arrivò a casa di Chiara, lei gli aprì la porta e il suo cane corse a salutarlo. Il cane di Chiara è enorme: è più o meno grande come Gianni! Quando Gianni vide l'enorme cane di Chiara disse: "Chiara, non hai affatto un cane. Hai un elefante!"

E' vero quello che ha detto Gianni?

Perché Gianni ha detto questo?

4)Un giorno, mentre stava giocando a casa, Anna accidentalmente rovesciò e ruppe il vaso di cristallo preferito di sua madre. Anna sapeva che la madre si sarebbe molto arrabbiata! Così, quando la madre ritornò a casa e vide il vaso rotto e chiese ad Anna cosa fosse successo, Anna disse: ”Il cane lo ha rovesciato, non è stata colpa mia!”

E’ vero quello che Anna ha raccontato alla madre?

Perché Anna ha detto questo?

5)Giovanni odia andare dal dentista, perché ogni volta che ci va deve fare un’otturazione che gli fa molto male. Ma Giovanni sa che quando ha mal di denti, sua madre lo porta sempre dal dentista Adesso Giovanni ha un forte mal di dente, ma quando sua madre nota che lui sta male e gli chiede: “Hai mal di dente Giovanni?”, Giovanni risponde: “No, mamma”.

E’ vero quello che Giovanni dice a sua madre?

Perché Giovanni dice questo?

6)Elena aspettava tutto l’anno Natale per chiedere ai suoi genitori un coniglietto. Arrivò il giorno di Natale ed Elena corse ad aprire il suo regalo. Era sicura che contenesse un piccolo coniglio nella gabbia. Ma quando lo aprì, con tutta la famiglia che stava intorno, scoprì che il suo regalo era una noiosa enciclopedia, che Elena non desiderava affatto! Poi, quando i genitori di Elena le chiesero quanto le era piaciuto il suo regalo di Natale, lei disse: “E’ bellissimo, grazie. E’ proprio quello che volevo”.

E’ vero quello che Elena ha detto?

Perché Elena ha detto questo ai suoi genitori?

7)Un giorno zia Lucia venne a visitare Pietro. Di solito a Pietro piace molto sua zia, ma quel giorno indossava un nuovo cappello che a Pietro non piaceva. Pietro pensava che sua zia sembrasse ridicola con quel cappello, e che sarebbe stata molto meglio con quello vecchio. Ma quando zia Lucia chiese a Pietro: ”Ti piace il mio nuovo cappello?” Pietro rispose: ”Oh, è molto bello”.

E’ vero quello che Pietro ha detto?

Perché Pietro lo ha detto?

8)A notte tarda la vecchia signora Bianchi sta tornando a casa. A lei non piace camminare verso casa da sola nel buio perché è sempre preoccupata che qualcuno l’aggredisca e la derubi. Improvvisamente da un ‘ombra sbuca un uomo. Vuole chiedere alla signora Bianchi che ora è, così cammina verso di lei. Quando la signora Bianchi vede l’uomo che cammina verso di lei, comincia a tremare e dice: ” Prenda la mia borsa, ma non mi faccia del male, per favore!”

L’uomo sarà rimasto sorpreso di quanto ha detto la signora Bianchi?

Perché lei gli ha detto questo, visto che lui voleva solo chiederle che ora era?

9)Un ladro che aveva appena rubato in un negozio si stava dando alla fuga. Mentre correva verso casa, un poliziotto di turno lo vide che perdeva un guanto. Il poliziotto non sapeva che l’uomo era un ladro, e voleva solo dirgli che aveva perso un guanto. Ma quando il poliziotto gridò al ladro: “Ehi, lei! Si fermi!”, il ladro si girò, vide il poliziotto e si arrese. Con le mani in alto ammise di aver compiuto il misfatto nel negozio.

Sarà rimasto sorpreso il poliziotto di quello che il ladro ha detto?

Perché il ladro si è comportato così, visto che il poliziotto voleva solo restituirgli il suo guanto?

10)Daniele e Luca un giorno vedono la signora Verdi che esce dal parrucchiere. Fa un po' ridere perché il parrucchiere le ha tagliato i capelli troppo corti. Daniele dice a Luca: "Deve esser stata in un combattimento con una falciatrice!"

E' vero quello che dice Daniele?

Perché Daniele dice questo?

11)Simone è un grande bugiardo e Massimo, il fratello di Simone, sa che Simone non dice mai la verità! Proprio ieri Simone ha rubato la racchetta di ping-pong di Massimo, e Massimo sa che Simone l'ha nascosta da qualche parte, nonostante non riesca a trovarla. E' molto arrabbiato. Così dice a Simone: "Dov'è la mia racchetta da ping-pong? Devi averla nascosta nell'armadio o sotto il letto, perché ho guardato ovunque. Dov'è, nell'armadio o sotto il letto?" Simone risponde che è sotto il letto.

Sarà vero quello che Simone ha detto a Massimo?

Dove cercherà Massimo la sua racchetta da ping-pong?

Perché cercherà lì la sua racchetta?

12)La madre di Anna ha trascorso molto tempo a cucinare il piatto preferito di Anna: pesce e patatine. Ma quando lo porta ad Anna, lei sta guardando la TV, non la bada e nemmeno la ringrazia. La madre di Anna è arrabbiata e dice:" Bene, questo è un bel comportamento, non trovi? Questa è per me pura maleducazione!"

E' giusto quello che ha detto la madre di Anna?

Perché la madre di Anna ha detto questo?

13)Marco e Filippo si stanno divertendo! Hanno rovesciato il tavolo per terra e si sono seduti sopra. Quando la loro madre ritorna, ride e dice: "Cosa mai state facendo?" "Questo tavolo è una nave pirata!", dice Filippo, "ed è meglio che tu entri prima di affogare, perché lì sei nel mare!"

E' vero quello che dice Filippo?

Perché Filippo dice questo?

TEST DI ATTRIBUZIONE DELLE EMOZIONI

Questo test consiste in una serie di brevissime scene con un protagonista. Alla fine di ogni scena, le si chiede di scrivere quale emozione proverà, secondo lei, il protagonista nella specifica situazione descritta.

1) I quadri di Simone sono arrivati ultimi ad un concorso. *Come si sentirà Simone in questa situazione?* _____

2) Elisabetta sta guidando lungo una strada quando una donna le compare improvvisamente davanti e lei la travolge in pieno. *Cosa proverà Elisabetta in questa situazione?*_____

3) Maria deve fare un discorso al lavoro. E' in piedi nella stanza di fronte a tutti. Non ricorda cosa deve dire. Tutti la fissano. *Come si sentirà Maria in questa situazione?*_____

4) Luca si è appena rivelato alla ragazza che desiderava da mesi. Lei gli dà uno schiaffo in faccia. *Come si sentirà Luca in questa situazione?*_____

5) Enrico ha appena scoperto che avrà un aumento della paga extra. *Come si sentirà Enrico in questa situazione*?_____

6) A Rosanna è stato appena detto dal suo fidanzato che lui non vuole più uscire con lei. *Come si sentirà Rosanna in questa situazione?*_____

7) Carlo è sdraiato in mezzo alla foresta. Un ragno velenoso cade sul suo petto. *Cosa proverà Carlo in questa situazione?* _____

8) Giuseppe ha appena saputo che il suo stipendio si ridurrà il prossimo mese. *Come si sentirà Giuseppe in questa situazione?*_____

9) Iris ha appena saputo che ha un cancro maligno che potrebbe ucciderla in meno di un anno *Cosa proverà Iris in questa situazione?*_____

10) Elena ordina un panino in un ristorante. Mangia il primo boccone e guarda il resto. C'è un verme morto nel panino. *Cosa proverà Elena in questa situazione?*_____

11) Paolo sente il suono che avvisa l'imminente caduta di una bomba atomica*. Cosa proverà Paolo in questa situazione?*_____

12) Un uomo cammina verso Andrea e lo chiama idiota*. Come si sentirà Andrea in questa situazione?*_____

13) A Tania venne detto che se avesse truccato il viso ad una donna le sarebbero state pagate 20.000 lire. Ma dopo che ebbe completato il lavoro le vennero date 10.000 lire*. Come si sentirà Tania in questa situazione?*_____

14) Fabio lancia un libro ad un suo amico. Il suo amico non lo prende e il libro finisce in faccia ad un altro uomo. *Cosa proverà Fabio in questa situazione?*_____

15) Roberto si sintonizza sulle radio notizie e sente che i suoi vicini hanno appena vinto 200 milioni alla lotteria. Il suo vicino sta raccontando al giornalista di tutti i viaggi che farà e di tutte le cose che comprerà. *Cosa proverà Roberto in questa situazione?*_____

16) Romina non vede suo marito da settimane. Poi lo vede nella strada e gli corre incontro. *Come si sentirà Romina in questa situazione?*_____

17) Daniele sta camminando in una strada affollata quando inciampa e sbatte con la faccia. Tutti nella strada si girano, lo fissano e cominciano a ridere. *Come si sentirà Daniele in questa situazione?*_____

18) Tania sta ascoltando i numeri della lotteria. Ha già segnato cinque numeri ed è prossima a vincere 10 milioni. *Come si sentirà Tania in questa situazione?*_____

19) Ogni settimana al lavoro di Giovanni sottraggono un premio a chiunque stia facendo peggio. Questa settimana è toccato a Giovanni. *Come si sentirà Giovanni in questa situazione?*_____

20) Katia ha ricevuto i risultati dei suoi esami: sono andati molto bene. *Come si sentirà Katia in questa situazione?*_____

21) Melania si trova in un vicolo. Un uomo sta andando verso di lei con un coltello. *Cosa proverà Melania in questa situazione?*_____

22) Elisabetta ha da poco un nuovo fidanzato. *Come si sentirà Elisabetta in questa situazione?*_____

23) La macchina di Riccardo, che ha 20 anni, si è appena rotta lungo la strada. Mentre sta seduto lì, qualcuno passa con una nuova Jaguar. Riccardo guarda la macchina che passa. *Come si sentirà Riccardo in questa situazione?*_____

24) Giulia sta in piedi in centro alla sala nuziale per tenere un discorso. Ma mentre è in pedi non le viene niente da dire. Tutti, nella sala, la fissano e qualcuno comincia a ridere. *Come si sentirà Giulia in questa situazione*?_____

25)Elisa vorrebbe un coniglietto per il suo compleanno, ma le è stato detto dai suoi genitori che le sarà donata una bicicletta, che però lei non vuole. Ma, quando scende per aprire il suo regalo, scopre che dentro c'è un coniglietto. *Come si sentirà Elisa in questa situazione?* _____

26)Silvia si sveglia e vede che c'è un ragno velenoso nel suo letto. *Cosa proverà Silvia in questa situazione?*_____

27) Giacomo si è appena preparato una scodella di corn flakes e latte. Ne mangia una cucchiaiata e si rende conto che il latte è andato a male. *Cosa proverà Giacomo in questa situazione?*_____

28) Sonia sta andando in bicicletta lungo la strada quando perde il controllo e finisce addosso ad un lampione. Alcune persone dall'altra parte della strada si fermano e la fissano; qualcuno la deride. *Come si sentirà Sonia in questa situazione?*_____

29)Un uomo cammina verso Massimo e minaccia di dargli un pugno. *Come si sentirà Massimo in questa situazione?*_____

30) William è appena andato al primo appuntamento con una ragazza di cui è interessato da quattro anni. Alla fine dell'appuntamento si baciano. *Come si sentirà William in questa situazione?*_____

31) Margherita ha appena scoperto che sua madre è morta. *Come si sentirà Margherita in questa situazione?*_____

32) A Giovanna è stata appena data una promozione. *Come si sentirà Giovanna in questa situazione?*_____

33) Sara ha parcheggiato all'angolo della strada quando una donna giunge e colpisce la sua auto con un martello, danneggiando parecchio il cofano. *Come si sentirà Sara in questa situazione?*_____

34) Rebecca sta tirando fuori dal frigo il pranzo della domenica quando si accorge che stanno strisciando dei vermi. *Cosa proverà Rebecca in questa situazione?*_____

35) Arturo sta parlando con un uomo che non conosce molto bene. L'uomo sta mangiando un panino. Mentre stanno parlando l'uomo sputa un pezzo di cibo nella giacca di Arturo. Arturo afferra l'uomo e gli strappa a pezzi la maglietta. *Come si sentirà Arturo in questa situazione?*_____

36) A Nadia venne detto che il suo prossimo lavoro sarebbe stato a Roma, la sua città preferita. Invece sarà a Padova, città che non le piace. *Come si sentirà Nadia in questa situazione*?_____

37) Giampaolo sta campeggiando nella foresta in America. Un orso strappa una parte della sua tenda e viene verso di lui ringhiando. *Cosa proverà Giampaolo in questa situazione?*_____

38) Ad Andrea, disoccupato, è stato appena offerto un nuovo lavoro. *Come si sentirà Andrea in questa situazione?*_____

39) Simone si accorge che l'uomo accanto a lui possiede l'orologio d'oro che lui vuole comprarsi da tre anni. Simone sa che non potrà permettersi quell'orologio per un altro po' di anni. *Cosa proverà Simone in questa situazione*?_____

40) L'amica di Sonia le disse che se avesse badato lei ai suoi figli lunedì lei avrebbe badato i figli di Sonia giovedì. Sonia il lunedì badò i figli dell'amica, ma il giovedì l'amica le disse che non poteva badare i figli di Sonia perché aveva un altro appuntamento. *Come si sarà sentita Sonia in questa situazione?*_____

41) Mario è stato chiamato dal suo capo. Questo gli dice: "Sei licenziato". *Come si sentirà Mario in questa situazione?*_____

42) La moglie di Daniele ha appena partorito il loro terzo figlio. *Come si sentirà la moglie di Daniele in questa situazione*?_____

43) Fulvio si trova in banca nel mezzo di una rapina. Uno dei rapinatori gli punta la pistola in faccia. *Come si sentirà Fulvio in questa situazione?*_____

44) Giusy corre dentro al cinema e non vede la porta di vetro. Ci corre contro. Tutti nella fila si girano e la fissano e qualcuno la deride. *Come si sentirà Giusy in questa situazione?*_____

45) Katia ha appena scoperto che le sono stati rubati 10 milioni e non può fare niente per averli indietro. *Come si sentirà Katia in questa situazione?*_____

46) Mauro si è svegliato e sente un ladro che si muove in casa. *Come si sentirà Mauro in questa situazione*?_____

47) Edy si trova in un bar quando scivola in una macchia di grasso e cade. Tutti nel bar lo fissano. *Come si sentirà Edy in questa situazione*?_____

48) Enrico sta camminando lungo una via del paese. Purtroppo non vede un ciottolo. La bici sbanda e lui cade nell'erba. Una macchina si ferma e tutti lo vedono cadere. *Cosa proverà Enrico in questa situazione?*_____

49) Ogni volta che Nicoletta tenta di lavorare al computer non ne trova uno libero al lavoro. *Cosa proverà Nicoletta in questa situazione?*_____

50) Alessandro sta guardando dalla ringhiera di un ponte. Improvvisamente comincia a scivolare e finisce dritto dentro al fiumiciattolo. Mentre si arrampica fuori dall'acqua si accorge che c'è un pullman pieno di turisti che lo stanno fissando. *Come si sentirà Alessandro in questa situazione?*_____

51) Gianni viene portato in un safari. L'auto si è rotta e adesso un grande rinoceronte lo sta attaccando. *Come si sentirà Gianni in questa situazione?*_____

52) Emilia sta camminando mano nella mano con il suo amante lungo la strada. Suo marito, improvvisamente, compare dietro l'angolo e li sorprende insieme. *Cosa proverà Emilia in questa situazione?*_____

53) Simone scopre un ladro mentre ruba il suo portafoglio dalla borsa. *Come si sentirà Simone in questa situazione?*_____

54) Filippo si era iscritto ad una gara di pesca e voleva vincere. Così comprò un grosso pesce dal pescivendolo. Purtroppo uno dei giudici era il proprietario del negozio. Quest'uomo racconta a tutti cosa ha fatto Filippo. *Cosa proverà Filippo in questa situazione?*_____

55) Il capo di Priscilla le ha detto di fare il suo lavoro in un certo modo. Poi, alla fine della giornata, dopo che lei ha lavorato per ore, egli cambia idea vuole qualcosa di differente. *Come si sentirà Priscilla in questa situazione?*_____

56) Paolo ha fatto un contratto con un uomo. Se spedisce all'uomo la sua collezione di dischi, l'uomo gli dà un'auto. Paolo spedisce all'uomo la sua collezione di dischi. L'uomo però non gli dà l'auto come stabilito. *Come si sentirà Paolo in questa situazione?*_____

57) A Matteo venne detto che avrebbe avuto il suo gioco preferito per Natale. Invece gli venne regalata un'enciclopedia. *Come si sarà sentito Matteo in questa situazione?* _____

58)I genitori di Anna si aspettano da lei tutti voti ottimi nei suoi esami. Lei apre la lettera dei risultati davanti a loro. Tutti vedono che ha preso appena sufficiente in ogni esame. Come si sentirà Anna in questa situazione?_____

QUESTIONNAIRES

FUNCTIONAL AND MORPHOLOGICAL CORRELATES OF COGNITIVE AND SOCIAL COGNITION IMPAIRMENT IN MULTIPLE SCLEROSIS
A LONGITUDINAL STUDY

Beck Depression Inventory (BDI)

ISTRUZIONI: Nel questionario vi sono 21 gruppi di definizioni. Legga con attenzione ciascun gruppo e da ognuno scelga la definizione che meglio descrive come si è sentito durante l'ultima settimana, oggi compreso. Segni con una crocetta il numero a lato dell'affermazione scelta. Se più dichiarazioni dello stesso gruppo sembrano andare egualmente bene, segni ognuna di esse. Si accerti di aver letto tutte le voci di ciascun gruppo prima di fare la sua scelta.

A. 0. Non mi sento triste.
1. Mi sento malinconico o triste.
2. Sono sempre malinconico o triste e non riesco a liberarmi di questa sensazione.
3. Sono così triste o infelice che non riesco a sopportarlo.

B. 0. Non sono particolarmente pessimista o scoraggiato circa il futuro.
1. Mi sento scoraggiato circa il futuro.
2a. Ho la sensazione di non desiderare nulla intensamente.
2b. Ho la sensazione che non uscirò mai dalle mie difficoltà.
3.Ho la sensazione che il futuro è senza speranza e le cose non possono migliorare.

C. 0. Non mi sento un fallito.
1. Ho la sensazione di aver fallito in proporzione maggiore rispetto ad una persona media.
2a. Ho la sensazione di aver concluso ben poco di valido o significativo.
2b. Se ripenso alla mia vita riesco a vedere solo una serie di fallimenti.
3.Ho la sensazione di essere un fallimento totale come persona.

D. 0. Non sono particolarmente insoddisfatto.
1a. Mi sento annoiato per la maggior parte del tempo.
1b. Non mi godo le cose come facevo un tempo.
2. Non traggo più soddisfazione da nulla.
3. Sono insoddisfatto o annoiato di tutto.

E. 0. Non mi sento particolarmente colpevole.
1. Mi sento cattivo o indegno per la maggior parte del tempo.
2. In pratica ora mi sento continuamente cattivo o indegno.
3. Ho la sensazione di essere molto cattivo o indegno.

F. 0. Non ho la sensazione di stare subendo una punizione.
1. Ho la sensazione che mi possa accadere qualcosa di brutto.
2. Ho la sensazione che sto subendo una punizione o che sarò punito.
3a.Sento di meritare una punizione.
3b.Voglio essere punito.

G. 0. Non mi sento deluso da me.
1. Sono deluso di me.
2. Non amo me stesso.
3. Sono disgustato di me stesso.

H. 0. Non credo di essere peggiore di altri.
1. Mi critico per la mia debolezza o per i miei errori.
2. Mi accuso per le mie colpe.
3. Mi accuso per le cose brutte che accadono.

I. 0. Non penso mai di farmi del male.
1. Mi vengono idee di farmi male, ma non le realizzerei mai.
2a. Sento che starei meglio se morissi.
2b. Sento che la mia famiglia starebbe meglio se fossi morto.
3a. Ho dei piani precisi per suicidarmi.
3b. Mi ucciderei se potessi.

J. 0. Non piango più del solito.
1. Ora piango più che in passato.
2. Ora piango continuamente, non riesco a smettere.
3. Un tempo riuscivo a piangere, ora non ci riesco anche se ho voglia di piangere.

K. 0. Non sono più irritato del solito.
1. Mi infastidisco e mi irrito più facilmente di un tempo.
2. Mi sento continuamente irritato.
3. Non riesco ad irritarmi neppure per le cose che mi infastidivano un tempo.

L. 0. Non ho perso interesse per le altre persone.
1. Ora ho meno interesse che nel passato per gli altri.
2. Ho perso la maggior parte dell'interesse per le altre persone e mi importa poco di loro.
3. Ho perso completamente interesse per gli altri e non mi importa nulla di loro.

M. 0. Prendo le decisioni nel solito modo.
1. Cerco di rimandare le decisioni.
2. Ho grandi difficoltà quando devo prendere decisioni.
3. Non riesco più a prendere nessuna decisione.

N. 0. Non credo di avere un aspetto peggiore del solito.
1. Sono preoccupato di apparire vecchio e non attraente.
2. Ho la sensazione che ci siano delle modificazioni permanenti nel mio aspetto e che mi fanno apparire non attraente.
3. Ho la sensazione di essere brutto o repellente.

O. 0. Riesco a lavorare quasi altrettanto bene che nel passato.
1a. Devo sforzarmi di più per cominciare a fare qualcosa.
1b. Non lavoro bene come una volta.
2. Devo fare uno sforzo notevole per eseguire qualsiasi lavoro.
3. Non riesco a lavorare per niente.

P. 0. Dormo bene come al solito.
1. Al mattino mi sveglio più stanco che nel passato.
2. Mi sveglio una o due ore prima del solito e mi riesce difficile riaddormentarmi.
3. Mi sveglio molto presto tutti i giorni e non riesco a dormire più di 5 ore.

Q. 0. Non mi stanco più del solito.
1. **Mi stanco più facilmente di un tempo.**
2. **Mi stanco quasi sempre, qualsiasi cosa faccia.**
3. **Sono troppo stanco per fare alcunché.**

R. 0. Ho lo stesso appetito del solito.
1. **Non ho un buon appetito come una volta.**
2. **Ora ho molto meno appetito.**
3. **Non ho per niente appetito.**

S. 0. Di recente non sono calato granché di peso.
1. **Ho perso più di due chili.**
2. **Ho perso più di quattro chili e mezzo.**
3. **Ho perso più di sei chili e mezzo.**

T. 0. Non mi preoccupo della salute più del solito.
1. **Mi preoccupo per le fitte e i dolori o per il mal di stomaco o per la stitichezza,**
2. **Mi preoccupo talmente di come mi sento o di quello che sento che mi è difficile pensare ad altre cose.**
3. **Sono completamente preso dalle preoccupazioni sulla mia salute e da quello che sento.**

U. 0. Non ho notato di recente alcun cambiamento riguardante il mio interesse per il sesso.
1. **Ho meno interesse di una volta per il sesso.**
2. **Ora ho molto meno interesse per il sesso.**
3. **Ho perso completamente interesse per il sesso.**

State-Trait Anxiety Inventory (STAI X-1)

ISTRUZIONI: di seguito sono riportate alcune frasi che le persone usano spesso per descriversi. Legga ciascuna frase e contrassegni con una crocetta la risposta che riflette come Lei si sente ADESSO, cioè in questo preciso momento, mentre sta iniziando a compilare questo test. Non ci sono risposte giuste o sbagliate. Risponda a tutte le domande. Non impieghi troppo tempo per rispondere alle domande e scelga la sua risposta tra le seguenti:

□1 = PER NULLA □2 = UN POCO □3 = ABBASTANZA □4 = MOLTISSIMO

		PER NULLA	UN POCO	ABBASTANZA	MOLTISSIMO
1.1	Mi sento calmo.....	□1	□2	□3	□4
1.2	Mi sento sicuro.....	□1	□2	□3	□4
1.3	Sono teso.....	□1	□2	□3	□4
1.4	Ho dei rimpianti.....	□1	□2	□3	□4
1.5	Mi sento tranquillo.....	□1	□2	□3	□4
1.6	Mi sento turbato.....	□1	□2	□3	□4
1.7	Sono attualmente preoccupato per possibili disgrazie.....	□1	□2	□3	□4
1.8	Mi sento riposato.....	□1	□2	□3	□4
1.9	Mi sento ansioso.....	□1	□2	□3	□4
1.10	Mi sento a mio agio.....	□1	□2	□3	□4
1.11	Mi sento sicuro di me.....	□1	□2	□3	□4
1.12	Mi sento nervoso.....	□1	□2	□3	□4
1.13	Sono agitato.....	□1	□2	□3	□4
1.14	Mi sento molto teso.....	□1	□2	□3	□4
1.15	Sono rilassato.....	□1	□2	□3	□4
1.16	Mi sento contento.....	□1	□2	□3	□4
1.17	Sono preoccupato.....	□1	□2	□3	□4
1.18	Mi sento sovraeccitato e scosso.....	□1	□2	□3	□4
1.19	Mi sento allegro.....	□1	□2	□3	□4
1.20	Mi sento bene.....	□1	□2	□3	□4

State-Trait Anxiety Inventory (STAI X-2)

ISTRUZIONI: legga ciascuna frase e contrassegni con una crocetta la risposta che riflette come Lei si sente ABITUALMENTE. Risponda pensando a come Lei è di solito, non al momento attuale. Risponda a tutte le domande scegliendo la risposta tra le seguenti:

□1 = QUASI MAI □2 = QUALCHE VOLTA □3 = SPESSO □4 = QUASI SEMPRE

		QUASI MAI	QUALCHE VOLTA	SPESSO	QUASI SEMPRE
2.1	Mi sento bene.....	□1	□2	□3	□4
2.2	Mi stanco facilmente.....	□1	□2	□3	□4
2.3	Mi sento come se dovessi piangere.....	□1	□2	□3	□4
2.4	Vorrei poter essere felice come sembrano gli altri.....	□1	□2	□3	□4
2.5	Spesso perdo delle occasioni perché non riesco a decidermi abbastanza in fretta.....	□1	□2	□3	□4
2.6	Mi sento riposato.....	□1	□2	□3	□4
2.7	Io sono calmo, tranquillo e padrone di me.....	□1	□2	□3	□4
2.8	Sento che le difficoltà si accumulano tanto da non poterle superare	□1	□2	□3	□4
2.9	Mi preoccupo troppo di cose che in realtà non hanno importanza.....	□1	□2	□3	□4
2.10	Sono felice.....	□1	□2	□3	□4
2.11	Tendo a considerare <<difficili>> le cose.....	□1	□2	□3	□4
2.12	Manco di fiducia in me stesso.....	□1	□2	□3	□4
2.13	Mi sento sicuro.....	□1	□2	□3	□4
2.14	Cerco di evitare di affrontare crisi o difficoltà.....	□1	□2	□3	□4
2.15	Mi sento stanco e depresso.....	□1	□2	□3	□4
2.16	Sono contento.....	□1	□2	□3	□4
2.17	Pensieri di scarsa importanza mi passano per la mente e mi infastidiscono.....	□1	□2	□3	□4
2.18	Vivo le delusioni con tanta partecipazione da non poter togliermele dalla testa.....	□1	□2	□3	□4
2.19	Sono una persona costante.....	□1	□2	□3	□4
2.20	Divento teso e turbato quando penso alle mie attuali preoccupazioni	□1	□2	□3	□4

SCALA DI VALUTAZIONE DELL'IMPATTO DELLA FATICA (MFIS)

La fatica è una sensazione di stanchezza e mancanza di energia che molte persone provano di tanto in tanto . Ma molti pazienti affetti da SM provano sensazioni di fatica più intense con maggiore frequenza e con maggiore impatto rispetto agli altri. La seguente è una lista di affermazioni che descrivono gli effetti della fatica. Si prega di leggere attentamente le affermazioni quindi cerchiare il numero che meglio indica quanto la fatica ha inciso su di voi nelle ultime 4 settimane.Si prega di rispondere a tutte le domande. Se non siete certi di quale risposta scegliere, scegliete quella che si avvicina maggiormente al vostro stato. Chiedete all'intervistatore di spiegarvi le parole o le frasi che non comprendete.

		Mai	Raramente	Qualch e volta	Spesso	Quasi sempre
1	Sono stato meno vigile	0	1	2	3	4
2	Ho avuto difficoltà a prestare attenzione per periodi lunghi di tempo	0	1	2	3	4
3	Non sono stato in grado di pensare in modo lucido	0	1	2	3	4
4	Sono stato maldestro e scoordinato	0	1	2	3	4
5	Sono stato smemorato	0	1	2	3	4
6	Ho dovuto rallentare la mia attività	0	1	2	3	4
7	Sono stato meno motivato a fare qualsiasi cosa richieda uno sforzo	0	1	2	3	4
8	Sono stato meno motivato a partecipare ad attività sociali	0	1	2	3	4
9	Sono stato limitato nelle mia capacità di fare cose fuori casa	0	1	2	3	4
10	Ho avuto problemi a compiere sforzi fisici per lunghi periodi	0	1	2	3	4
11	Ho avuto difficoltà a prendere decisioni	0	1	2	3	4
12	Sono stato poco motivato nel compiere qualsiasi cosa che richieda di pensare intensamente	0	1	2	3	4
13	Sento i miei muscoli molto deboli	0	1	2	3	4
14	Sono stato male fisicamente	0	1	2	3	4
15	Ho avuto problemi a portare a termine compiti che richiedano	0	1	2	3	4
16	Ho avuto difficoltà nell'organizzare i miei pensieri	0	1	2	3	4
17	Ho avuto maggiori difficoltà del solito a concludere compiti che richiedano uno sforzo fisico	0	1	2	3	4
18	La mia capacità di ragionamento è risultata piuttosto rallentata	0	1	2	3	4
19	Ho avuto problemi di concentrazione	0	1	2	3	4
20	Ho limitato le mie attività fisiche	0	1	2	3	4
21	Ho avuto necessità di riposarmi più spesso del solito o per periodi più	0	1	2	3	4

Symptom Check-List - 90 (SCL-90)

Nella lista che segue sono elencati problemi e disturbi che spesso affliggono le persone. Li legga attentamente e cerchi di ricordare se ne ha sofferto nella scorsa settimana, oggi compreso, e con quale intensità. Risponda a tutte le domande facendo una crocetta nella casella corrispondente all'intensità di ciascun disturbo. Se sbaglia o cambia idea corregga in maniera chiara e comprensibile.

	IN CHE MISURA SOFFRE O HA SOFFERTO DI	*per niente*	*poco*	*moderatamente*	*molto*	*moltissimo*
1.	***Mal di testa***	0	1	2	3	4
2.	***Nervosismo o agitazione interna***	0	1	2	3	4
3.	***Incapacità a scacciare pensieri, parole o idee indesiderate***	0	1	2	3	4
4.	***Sensazione di svenimento o di vertigini***	0	1	2	3	4
5.	***Perdita dell'interesse o del piacere sessuale***	0	1	2	3	4
6.	***Tendenza a criticare gli altri***	0	1	2	3	4
7.	***Convinzione che gli altri possano controllare i suoi pensieri***	0	1	2	3	4
8.	***Convinzione che gli altri siano responsabili dei suoi disturbi***	0	1	2	3	4
9.	***Difficoltà a ricordare le cose***	0	1	2	3	4
10.	***Preoccupazioni per la sua negligenza o trascuratezza***	0	1	2	3	4
11.	***Sentirsi facilmente infastidito o irritato***	0	1	2	3	4
12.	***Dolori al cuore o al petto***	0	1	2	3	4
13.	***Paura degli spazi aperti o delle strade***	0	1	2	3	4
14.	***Sentirsi debole o fiacco***	0	1	2	3	4
15.	***Idee di togliersi la vita***	0	1	2	3	4
16.	***Udire voci che le altre persone non odono***	0	1	2	3	4
17.	***Tremori***	0	1	2	3	4
18.	***Mancanza di fiducia negli altri***	0	1	2	3	4
19.	***Scarso appetito***	0	1	2	3	4
20.	***Facili crisi di pianto***	0	1	2	3	4
21.	***Sentirsi intimidito nei confronti dell'altro sesso***	0	1	2	3	4
22.	***Sensazione di essere preso in trappola***	0	1	2	3	4
23.	***Paure improvvise senza ragione***	0	1	2	3	4
24.	***Scatti d'ira incontrollabili***	0	1	2	3	4
25.	***Paura di uscire da solo***	0	1	2	3	4

	IN CHE MISURA SOFFRE O HA SOFFERTO DI	*per niente*	*poco*	*moderatamente*	*molto*	*moltissimo*
26.	***Rimproverarsi per qualsiasi cosa***	0	1	2	3	4
27.	***Dolori alla schiena***	0	1	2	3	4
28.	***Senso di incapacità a portare a termine le cose***	0	1	2	3	4
29.	***Sentirsi solo***	0	1	2	3	4
30.	***Sentirsi giù di morale***	0	1	2	3	4
31.	***Preoccuparsi eccessivamente per qualsiasi cosa***	0	1	2	3	4
32.	***Mancanza di interesse***	0	1	2	3	4
33.	***Senso di paura***	0	1	2	3	4
34.	***Sentirsi facilmente ferito o offeso***	0	1	2	3	4
35.	***Convinzione che gli altri percepiscano i suoi pensieri***	0	1	2	3	4
36.	***Sensazione di non trovare comprensione o simpatia***	0	1	2	3	4
37.	***Sensazione che gli altri non le siano amici o l'abbiano in antipatia***	0	1	2	3	4
38.	***Dover fare le cose molto lentamente per essere sicuro di farle bene***	0	1	2	3	4
39.	***Palpitazioni o sentirsi il cuore in gola***	0	1	2	3	4
40.	***Senso di nausea o di mal di stomaco***	0	1	2	3	4
41.	***Sentimenti di inferiorità***	0	1	2	3	4
42.	***Dolori muscolari***	0	1	2	3	4
43.	***Sensazione che gli altri la guardino o parlino di lei***	0	1	2	3	4
44.	***Difficoltà ad addormentarsi***	0	1	2	3	4
45.	***Bisogno di controllare ripetutamente ciò che fa***	0	1	2	3	4
46.	***Difficoltà a prendere decisioni***	0	1	2	3	4
47.	***Paura di viaggiare in autobus, nella metropolitana o in treno***	0	1	2	3	4
48.	***Sentirsi senza fiato***	0	1	2	3	4
49.	***Vampate di calore o brividi di freddo***	0	1	2	3	4
50.	***Necessità di evitare certi oggetti, luoghi o attività perché la spaventano***	0	1	2	3	4
51.	***Senso di vuoto mentale***	0	1	2	3	4
52.	***Intorpidimento o formicolio di alcune parti del corpo***	0	1	2	3	4
53.	***Nodo alla gola***	0	1	2	3	4
54.	***Guardare al futuro senza speranza***	0	1	2	3	4

	IN CHE MISURA SOFFRE O HA SOFFERTO DI	*per niente*	*poco*	*moderatamente*	*molto*	*moltissimo*
55.	***Difficoltà a concentrarsi***	0	1	2	3	4
56.	***Senso di debolezza in qualche parte del corpo***	0	1	2	3	4
57.	***Sentirsi teso o sulle spine***	0	1	2	3	4
58.	***Senso di pesantezza alle braccia o alle gambe***	0	1	2	3	4
59.	***Idee di morte***	0	1	2	3	4
60.	***Mangiare troppo***	0	1	2	3	4
61.	***Senso di fastidio quando la gente la guarda o parla di lei***	0	1	2	3	4
62.√	***Avere dei pensieri che non sono suoi***	0	1	2	3	4
63.	***Sentire l'impulso di colpire, ferire o fare male a qualcuno***	0	1	2	3	4
64.	***Svegliarsi presto al mattino senza riuscire a riaddormentarsi***	0	1	2	3	4
65.	***Avere bisogno di ripetere lo stesso atto, come toccare, contare, lavarsi le mani, ecc.***	0	1	2	3	4
66.	***Sonno inquieto o disturbato***	0	1	2	3	4
67.	***Sentire l'impulso di rompere gli oggetti***	0	1	2	3	4
68.	***Avere idee o convinzioni che gli altri non condividono***	0	1	2	3	4
69.	***Sentirsi penosamente imbarazzato in presenza di altri***	0	1	2	3	4
70.	***Sentirsi a disagio tra la folla, come nei negozi, al cinema, ecc.***	0	1	2	3	4
71.	***Sensazione che tutto richieda uno sforzo***	0	1	2	3	4
72.	***Momenti di terrore o di panico***	0	1	2	3	4
73.	***Sentirsi a disagio quando mangia o beve in presenza di altri***	0	1	2	3	4
74.	***Ingaggiare frequenti discussioni***	0	1	2	3	4
75.	***Sentirsi a disagio quando è solo***	0	1	2	3	4
76.	***Convinzione che gli altri non l'apprezzino***	0	1	2	3	4
77.	***Sentirsi solo e triste anche in compagnia***	0	1	2	3	4
78.	***Senso di irrequietezza, tanto da non poter star seduto***	0	1	2	3	4
79.	***Sentimenti di inutilità***	0	1	2	3	4
80.	***Sensazione che le cose più comuni e familiari siano estranee o irreali***	0	1	2	3	4
81.	***Urlare e scagliare oggetti***	0	1	2	3	4
82.	***Avere paura di svenire davanti agli altri***	0	1	2	3	4
83.	***Impressione che gli altri possano approfittare delle sue azioni***	0	1	2	3	4

	IN CHE MISURA SOFFRE O HA SOFFERTO DI	*per niente*	*poco*	*moderatamente*	*molto*	*moltissimo*
84.	***Pensieri sul sesso che lo affliggono***	0	1	2	3	4
85.	***Idea di dover scontare i propri peccati***	0	1	2	3	4
86.	***Sentirsi costretto a portare a termine ciò che ha iniziato***	0	1	2	3	4
87.	***Pensiero di avere una grave malattia fisica***	0	1	2	3	4
88.	***Non sentirsi mai vicino alle altre persone***	0	1	2	3	4
89.	***Sentirsi in colpa***	0	1	2	3	4
90.	***Idea che qualche cosa non vada bene nella sua mente***	0	1	2	3	4

MSQOL-54

Edizione Italiana

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Modulo specifico MSQOL-54, versione originale B. Vickrey, 1995; versione Italiana A. Solari, Istituto Nazionale Neurologico C. Besta, Via Celoria 11, 20133 Milano 1998 (1)

ISTRUZIONI: Il questionario intende valutare cosa lei pensa della sua salute. Le informazioni raccolte permetteranno di essere aggiornati su come si sente e su come riesce a svolgere le sue attività' consuete.

Risponda a ciascuna domanda del questionario indicando la sua risposta come mostrato di volta in volta. Se non si sente certa della risposta, effettui la scelta che comunque le sembra migliore.

1. In generale, direbbe che la sua salute è:

(Indichi un numero)

Eccellente 1

Molto buona 2

Buona 3

Passabile 4

Scadente 5

2. Rispetto ad un anno fa, come giudicherebbe, ora, la sua salute in generale?

(Indichi un numero)

Decisamente migliore adesso rispetto ad un anno fa 1
Un po' migliore adesso rispetto ad un anno fa 2
Più o meno uguale rispetto ad un anno fa 3
Un po' peggiore adesso rispetto ad un anno fa 4
Decisamente peggiore adesso rispetto ad un anno fa 5

Le seguenti domande riguardano alcune attività che potrebbe svolgere nel corso di una qual- siasi giornata. La sua salute la limita attualmente nello svolgimento di queste attività?

3. La sua salute la limita attualmente nello svolgimento di **attività fisicamente impegnative**, come correre, sollevare oggetti pesanti, praticare sport faticosi?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

4. La sua salute la limita attualmente nello svolgimento di **attività di moderato impegno fisico**, come spostare un tavolo, usare l'aspirapolvere, giocare a bocce o fare un giretto in bicicletta ?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

5. La sua salute la limita attualmente nel **sollevare o portare le borse della spesa**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

6. La sua salute la limita attualmente nel **salire qualche piano di scale**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

7. La sua salute la limita attualmente nel **salire un piano di scale**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

8. La sua salute la limita attualmente nel **piegarsi, inginocchiarsi o chinarsi**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

9. La sua salute la limita attualmente nel **camminare per un chilometro**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

10. La sua salute la limita attualmente nel **camminare per qualche centinaia di metri**?

(Indichi un numero)

SI, mi limita parecchio 1
SI, mi limita parzialmente 2
NO, non mi limita per nulla 3

11. La sua salute la limita attualmente nel **camminare per circa cento metri**?

(Indichi un numero)

SI, mi limita parecchio 1

SI, mi limita parzialmente 2

NO, non mi limita per nulla 3

12. La sua salute la limita attualmente nel **fare il bagno o vestirsi da sola**?

(Indichi un numero)

SI, mi limita parecchio 1

SI, mi limita parzialmente 2

NO, non mi limita per nulla 3

Nelle ultime 4 settimane, ha riscontrato i seguenti problemi sul lavoro o nelle altre attività quotidiane, a causa della sua salute fisica?

Risponda SI o NO a ciascuna domanda.

13. Nelle ultime 4 settimane, a causa della sua salute fisica ha ridotto **il tempo dedicato al lavoro o ad altre attività**?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

14. Nelle ultime 4 settimane, a causa della sua salute fisica ha reso **meno di quanto avrebbe voluto**?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

15. Nelle ultime 4 settimane, a causa della sua salute fisica ha dovuto **limitare alcuni tipi di lavoro o altre attività**?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

16. Nelle ultime 4 settimane, a causa della sua salute fisica ha avuto **difficoltà nell'eseguire il lavoro o altre attività** (ad esempio, ha fatto più fatica?)

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

Nelle ultime 4 settimane, ha riscontrato i seguenti problemi sul lavoro o nelle altre attività quotidiane, a causa del suo stato emotivo (quale il sentirsi depressa o ansiosa)?

Risponda SI o NO a ciascuna domanda.

17. Nelle ultime 4 settimane, a causa del suo stato emotivo ha ridotto il **tempo dedicato al lavoro o ad altre attività**?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

18. Nelle ultime 4 settimane, a causa del suo stato emotivo ha **reso meno di quanto avrebbe voluto**?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

19. Nelle ultime 4 settimane, a causa del suo stato emotivo ha avuto **un calo di concentrazione** sul lavoro o in altre attività?

(Indichi per ogni domanda il numero 1 o 2)

SI 1

NO 2

20. Nelle ultime 4 settimane, in che misura la sua salute fisica o il suo stato emotivo hanno **interferito con le normali attività sociali** con la famiglia, gli amici, i vicini di casa, i gruppi di cui fa parte?

(Indichi un numero)

Per nulla 1

Leggermente 2

Un po' 3

Molto 4

Moltissimo 5

21. Quanto **dolore fisico** ha provato nelle ultime 4 settimane?

(Indichi un numero)

Nessuno 1

Molto lieve 2

Lieve 3

Moderato 4

Forte 5

Molto forte 6

22. Nelle ultime 4 settimane, in che misura il **dolore l'ha ostacolata** nel lavoro che svolge abitualmente (sia in casa sia fuori casa)?

(Indichi un numero)

Per nulla 1
Molto poco 2
Un po' 3
Molto 4
Moltissimo 5

Le seguenti domande si riferiscono a come si è sentita nelle ultime 4 settimane. Risponda a ciascuna domanda scegliendo la risposta che più si avvicina al suo caso.

23. Per quanto tempo nelle ultime 4 settimane si è sentita **vivace e brillante**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

24. Per quanto tempo nelle ultime 4 settimane si è sentita **molto agitata**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

25. Per quanto tempo nelle ultime 4 settimane si è sentita così **giù di morale** che niente avrebbe potuto tirarla su?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

26. Per quanto tempo nelle ultime 4 settimane si è sentita **calma e serena**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

27. Per quanto tempo nelle ultime 4 settimane si è sentita **piena di energia**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

28. Per quanto tempo nelle ultime 4 settimane si è sentita **scoraggiata e triste**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

29. Per quanto tempo nelle ultime 4 settimane si è sentita **sfinita**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

30. Per quanto tempo nelle ultime 4 settimane si è sentita **felice**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

31. Per quanto tempo nelle ultime 4 settimane si è sentita **stanca**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

32. Nelle ultime 4 settimane, per quanto tempo la sua salute fisica o il suo stato emotivo hanno interferito nelle sue **attività sociali**, in famiglia, con gli amici?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Una parte del tempo 3
Quasi mai 4
Mai 5

Scelga la risposta che meglio descrive quanto siano **VERE o FALSE** le seguenti affermazioni.

33. Mi pare di ammalarmi un po' più facilmente degli altri

(Indichi un numero)

Certamente vero 1
In gran parte vero 2
Non so 3
In gran parte falso 4
Certamente falso 5

34. La mia salute è come quella degli altri

(Indichi un numero)

Certamente vero 1
In gran parte vero 2
Non so 3
In gran parte falso 4
Certamente falso 5

35. Mi aspetto che la mia salute andrà **peggiorando**

(Indichi un numero)

Certamente vero 1
In gran parte vero 2
Non so 3
In gran parte falso 4
Certamente falso 5

36. Godo di **ottima salute**

(Indichi un numero)

Certamente vero 1
In gran parte vero 2
Non so 3
In gran parte falso 4
Certamente falso 5

37. Nelle ultime 4 settimane, per quanto tempo si è sentita **riposata** al suo risveglio al mattino?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

38. Nelle ultime 4 settimane, per quanto tempo si è sentita **scoraggiata** a causa della sua salute?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

39. Nelle ultime 4 settimane, per quanto tempo si è sentita **frustrata** a causa della sua salute?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

40. Nelle ultime 4 settimane, per quanto tempo si è sentita **preoccupata** a causa della sua salute?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

41. Nelle ultime 4 settimane, per quanto tempo si è sentita **oppressa** a causa della sua salute?

(Indichi un numero)

Sempre..... 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai..... 5
Mai 6

42. Nelle ultime 4 settimane, per quanto tempo ha provato **difficoltà di concentrazione e di ragionamento**?

(Indichi un numero)

Sempre..... 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai..... 5
Mai 6

43. Nelle ultime 4 settimane, per quanto tempo ha trovato difficile mantenere la sua
attenzione a lungo durante lo svolgimento di una attività?

(Indichi un numero)

Sempre..... 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai..... 5
Mai 6

44. Nelle ultime 4 settimane, per quanto tempo ha avuto difficoltà a **ricordare**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

45. Nelle ultime 4 settimane, per quanto tempo altre persone (familiari o amici) le hanno fatto notare che ha difficoltà a **ricordare ed a concentrarsi**?

(Indichi un numero)

Sempre 1
Quasi sempre 2
Molto tempo 3
Una parte del tempo 4
Quasi mai 5
Mai 6

Le prossime domande riguardano la sua attività sessuale ed il suo grado di soddisfazione. Risponda a ciascuna domanda scegliendo la risposta che più si avvicina al suo caso.

Consideri solo le ultime 4 settimane.

46. Nelle ultime 4 settimane, in che misura la **mancanza di stimoli sessuali** ha rappresentato un problema per lei?

(Indichi un numero)

Nessun problema 1

In piccola parte un problema 2

In parte un problema..... 3

In gran parte un problema..... 4

47. Nelle ultime 4 settimane, in che misura **l'insufficiente lubrificazione** ha rappresentato un problema per lei?

(Indichi un numero)

Nessun problema 1

In piccola parte un problema 2

In parte un problema..... 3

In gran parte un problema..... 4

48. Nelle ultime 4 settimane, in che misura la difficoltà nel **raggiungere l'orgasmo**
ha rappresentato un problema per lei?

(Indichi un numero)

Nessun problema 1

In piccola parte un problema 2

In parte un problema..... 3

In gran parte un problema..... 4

49. Nelle ultime 4 settimane, in che misura la capacità di **soddisfare sessualmente il partner** ha rappresentato un problema per lei?

(Indichi un numero)

Nessun problema 1
In piccola parte un problema 2
In parte un problema 3
In gran parte un problema 4

50. In generale, quale è stato il suo livello di **soddisfazione rispetto alla sua attività sessuale** nelle ultime 4 settimane?

(Indichi un numero)

Molto soddisfatta 1
Abbastanza soddisfatta 2
Né soddisfatta né insoddisfatta 3
Piuttosto insoddisfatta 4
Molto insoddisfatta 5

51. Nelle ultime 4 settimane, i **disturbi urinari o intestinali** le hanno impedito di svolgere le sue normali attività di relazione con i familiari, con gli amici, con i vicini o nei gruppi di cui fa parte?

(Indichi un numero)

Per nulla 1
Leggermente 2
Un po' 3
Molto 4
Moltissimo 5

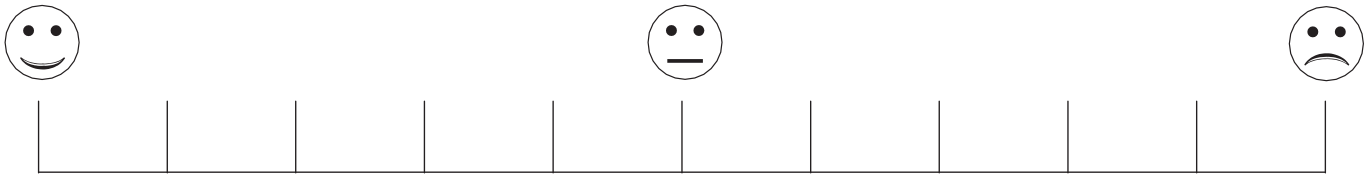
52. Nelle ultime 4 settimane, in che misura la sua vita è stata compromessa dal **dolore fisico**?

(Indichi un numero)

Per nulla 1
Leggermente 2
Un po' 3
Molto 4
Moltissimo 5

53. In termini generali, come giudicherebbe la qualità della sua vita?

(Indichi un numero nella scala)



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Migliore qualità della vita

Peggiore qualità della vita possibile (simile alla morte o peggio)

54. Quale dei seguenti termini descrive meglio come si sente se pensa alla sua vita, nel suo insieme?

(Indichi un numero)

Malissimo 1
Scontenta 2
In gran parte insoddisfatta 3
Tanto soddisfatta quanto insoddisfatta allo stesso modo 4
In gran parte soddisfatta 5
Contenta 6
Benissimo 7