Multiple Sclerosis

DESCRIPTION

Multiple sclerosis (MS) is a degenerative and autoimmune condition that affects 100–130 per 100,000 people in the United States (Kurtzke & Wallin, 2000). Currently, MS is considered one of the most prevalent chronic neurological disorders in young and middle adulthood, with a peak incidence in the third decade and the highest prevalence within 40–59 years of age. Women present a higher tendency to develop MS with an average ratio of 2.6:1. The clinical presentation of MS is caused primarily by demyelination (destruction of the myelin sheath), with associated inflammation and visible white matter lesions in magnetic resonance studies being a prominent feature. Etiological causes of MS are still unknown; however, the interaction of genetic and environmental factors has been postulated as most important susceptibility agents (Ebers, 2008). There is a latitudinal variation in the prevalence of MS, being reportedly more frequent in areas more distant from the Equator and mounting evidence between the inverse relation between sun exposure and the development of MS (MacLean & Freedman, 2009). MS presentation is characterized by episodes of focal deficits of the optic nerves, and spinal cord and brain injury that usually require medical attention and that might remit and recur sporadically for years. Clinical symptoms in MS include motor weakness, paraparesis (motor weakness on lower extremities), vision changes, diplopia, nystagmus, dysarthria, intention tremor, ataxia, somatosensory changes (paresthesias), and bladder dysfunction. Other important and common, but sometimes underreported, symptoms include cognitive and affective changes (Haase, Tinnefeld, Lieneman, Ganz, & Faustmann, 2003). Diagnosis in MS is difficult due to the relapsing and remitting pattern, the subtle nature of symptoms and the apparent similarity with other diseases especially autoimmune ones. MS subtypes have been identified as relapsing–remitting MS (RRMS), progressive relapsing, primary progressive, and secondary progressive. The most aggressive and likely type to produce morbidity is primary progressive. Another important clinical category within the MS spectrum is the clinically isolated syndrome (CIS) an isolated CNS syndrome (optic neuritis, incomplete transverse myelitis, brainstem or cerebellar lesion), which is often the first MS attack (Thrower, 2007). The use of MRI has enlightened our knowledge of this disease and has replaced other studies used in the past to aid in the diagnosis of MS. Earlier diagnosis is now possible with its routine use (Bakshi, Hutton, Miller, & Radue, 2004).

Treatment methods in MS aim to decrease the possibility of new clinical relapses or slowing of the progression of the disease by MRI. The first method of treatment is through interferons, which are naturally occurring antiviral proteins. Glatiramer acetate, which acts in the immune system to spare myelin from further attack, has shown to alter the natural history of RRMS. Natalizumab, and chemotherapeutic agents are used in secondary progressive MS, and other less conventional therapies are intravenous corticosteroids intravenous immunoglobulin or plasma exchange. In MS, neuropsychology presents an important

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(MS), chronic, slowly progressive autoimmune disease in which the body's immune system attacks the protective myelin sheaths that surround the nerve

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Multiple sclerosis is an often crippling disease of the central nervous system that afflicts an estimated 150,000 to

bridge between the physical (e.g., brain lesions) and cognitive and emotional (e.g., memory and depression) areas. In doing so, the Cartesian dualism is hinged to form one continuum. The end result of neuropsychological assessment is heightened understanding and advanced treatment of the patient with MS.

NEUROPATHOLOGY/PATHOPHYSIOLOGY

MS is largely an inflammatory demyelinating autoimmune disease that is thought to develop by a combination of genetic and environmental factors. Pathologic damage is caused by T lymphocytes that become activated and gain entrance to the blood–brain barrier. This entrance causes an inflammatory response that in turn attacks the myelin. During the disease process, only central myelin produced by oligodendrocytes is affected, which causes astrocytes to respond by forming a glial scar. These patches of demyelination in the white matter of the brain or spinal cord disrupt central nerve transmission. Pathologic studies along with more advanced neuroimaging techniques indicate axonal damage and neuronal loss that eventually lead to brain atrophy. Axon loss is the major cause of irreversible disability in patients with MS (Dutta & Trapp, 2007). Antibody- and complement-mediated myelin phagocytosis (macrophages engulfing cellular debris), in this case myelin, is also a pathophysiological process occurring later in the degenerative process of this disease (Dhib-Jalbut, 2007). These disease processes have been well documented in postmortem specimens of MS patients.

Neurobiological Markers

Many biological markers have been studied in MS, and the most widely used markers are those obtained through a spinal tap from the CSF like myelin basic protein (MBP), immunoglobulin (IgG) index, and oligoclonal bands (OGCB). The genetic region most clearly associated with MS susceptibility is the human leukocyte antigen (HLA) locus on the short arm of chromosome 6 (6p21) (De Jager et al., 2008). In various studies, the HLA region has been estimated to confer somewhere between 10% and 50% of the inheritability of MS. In Caucasian MS populations of northern European descent, the critical MS-associated genetic region is thought to reside near the class II *locus and is comprised of a group of genes with specific alleles that tend to occur in certain fixed combinations termed haplotypes. In molecular terms, the “DR2” haplotype is designated as HLA-DRB1*1501, DQA1*0102, and DQB1*0602. These DR molecules are comprised of alpha and beta chains (encoded by A and B genes, respectively), and the polymorphisms are predominantly present in the beta chain. Of the more than 100 beta-chain sequence variations identified in humans, only one (1501, also designated as DR2) is associated with MS, and the DR2 gene is the most important genetic contributor to MS susceptibility identified to date.

Neuroimaging Techniques

MRI can be used to demonstrate dissemination in space and time within the brain and spinal cord, which has led to its common use as a paraclinical measure for diagnosis of MS including diagnosing patients with CIS. In addition, MRI is used to monitor the progress of disease in patients with clinically definite MS, including assessment of lesions and atrophy (Bakshi et al., 2004). Several MRI techniques can be used to study MS (Table 1). The most important ones, required for diagnosis are T2-weighted images (showing areas of demyelination and edema) and gadolinium-enhanced (T1) images (indicating the presence of acute inflammation). T1 images also help to determine the presence of “black holes” or axonal damage. On T2 and FLAIR, MS lesions are seen as hyperintense, ovoid-shaped, periventricular white matter lesions oriented perpendicular to the ventricular surface (known as Dawson's fingers). They also commonly appear as corpus callosal, juxtacortical, and infratentorial lesions involving the posterior fossa and spinal cord.

Table 1 Information Provided by MRI

Techniques	Importance
T1	Gadolinium-enhancing lesions detect blood–brain barrier leakage, inflammatory disturbances, and recent (≤6 weeks) activity, with lesion formation.
	Hypointense lesions (black holes) reflect more severe tissue pathology, including axon loss and correlates with disability.
T2	Hyperintense lesions provide total burden of disease measure, including reversible and irreversible pathologies. Most predictive of disease course in early MS. Hyperintense T2 lesions can reflect a variety of pathologic processes in addition to demyelination, such as inflammation, edema, axonal loss, and remyelination
Diffusion-weighted	Detects abnormalities in both lesions and normal-appearing CNS tissue. Detects white matter changes.
Flair (fluid attenuated inversion recovery)	Hyperintense lesions

Not widely available but useful in the evaluation of MS patients is the functional MRI that helps to evaluate neuronal circuits needed for diverse brain functions. It measures critical circuitry involved in response to injury, activation, loss of function, and recovery of function. Magnetic resonance spectroscopy (MRS) is another MRI technique that has gained much interest in recent years because it can be used to detect early abnormalities even in otherwise normal-appearing brain tissue. Studies have shown that decreased *N*-acetyl aspartate (NAA) levels reflect axon damage that is an important cause of disability. NAA is a biochemical found in neurons considered an index of axonal integrity and functional activity. In 2003, Cristodoulou et al. found a correlation between neuropsychological symptoms and NAA/Cr ratios on the brain central ventricular areas, with a higher correlation on the right hemisphere. Some researchers hypothesize that the cognitive and emotional symptoms observed at early stages of the disease could be more related to early biochemical changes than to structural damage caused by lesions and inflammation (Benedict, Weinstock-Guttman, Fishman, Sharma, & Tjoa, 2004).

Magnetic Resonance Spectroscopy in MS

MRS is a noninvasive neuroimaging technique that allows the in vivo quantification of brain neurochemistry by measuring concentration of key metabolites (Stanley, 2002) like NAA, mio-inositol, choline, and Cr. Over the past 20 years, MRS has been used to study the pathological mechanisms of neurological and psychiatric disorders, monitor long-term changes, identify differences among diagnostic groups, and study cognitive dysfunction on these disorders (Ross & Sachdev, 2004). The relative quantity or amount of these metabolites is usually determined by comparing their resonance peaks. Other methods like event-related potentials, brain size volume, cerebral metabolic rate, and cerebral blood flow have not been found to be strongly associated with cognitive functions, and due to cerebral plasticity measures of neural integrity such as MRS, should be the most sensitive to the neuropathology that leads to cognitive decline (Zivadinoff & Bakshi, 2004). Interestingly, in MS these lowered levels of NAA do not correlate with the total amount of lesions (Fillipi et al., 2003), which are critical in the diagnosis of MS criteria (McDonald, Compston, & Edan, 2001). This represents an important finding and might support the cognitive/neuropsychological deficits that have been observed in MS patients in early stages of the disease.

Diffusion Weighted Imaging and Diffusion-Tensor Imaging in MS

The magnetic resonance signal is intrinsically sensitive to motion at the molecular level. Two complementing MRI techniques known as diffusion-weighted and diffusion tensor-imaging (DWI and DTI) are capable of measuring water diffusion[1] and diffusion anisotropy[2]. Of particular relevance for the study of MS neuropathology is the fact that these diffusion-based MRI techniques are capable of characterizing white matter integrity and the orientation of white matter fiber bundles.

Increased water diffusion serves as a marker for cell membrane disruption. Moderate correlations have been found for DTI diffusivity and fractional anisotropy (FA) and cognitive functions on normal appearing gray matter and normal appearing white matter (Rovaris et al., 2002). Moreover, longitudinal studies using DTI[3] and mean diffusivity have found progressive microstructural changes after 18 months in the normal appearing matter that do not correlate with lesions and atrophy (Ojera et al., 2005). Water diffusion is restricted within intact white matter fibers. It is inferred that the more anisotropic the water diffusion is in a particular region of the brain, the more restricted it is and the higher the probability that it is constrained within intact tissue. By measuring the degree of directional anisotropy of diffusion, the DTI technique probes tissue integrity on a microscopic scale that is not possible to achieve using conventional anatomical MRI techniques such as those used for clinical diagnosis of MS.

The most recent DTI data on MS patients have shown that normal appearing white matter showed significant increased diffusivity as measured by the Apparent Diffusion Coefficient (ADC) and reduced FA compared with controls, whereas ADC had a stronger association to clinical disability than lesion load (Vrenken et al., 2006). Another recent study, with 23 early onset MS patients, showed decreased FA on normal-appearing white matter, which confirms occult tissue damage (Tortorella et al., 2006). In view of the most recent studies and metabolite quantification with MRS, DTI seems to be, for the moment, one of the most promising neuroimaging techniques available for the study of diffuse white matter degeneration. DTI is susceptible to subtle global tissue degeneration at a microscopic scale in otherwise normal appearing white matter using conventional anatomical MRI techniques, and it could become a potential diagnostic marker for MS at preclinical or early clinical stages (Table 1).

Spinal Tap

Spinal tap is a relatively easy procedure that can be done in MS patients to exclude any other infectious or inflammatory process that could mimic MS. CSF is taken for analysis that includes markers that aid in the diagnosis of the disease (Table 2).

Evoked Potentials

Evoked potentials (EPs) are electrodiagnostic studies that aid in the diagnosis of MS when history, clinical findings, or imaging studies do not confirm it and more evidence is needed. EPs evaluate processing pathways of sensory nerve tracts in the spinal cord, thalamus, and sensory cortex, auditory pathways in the brainstem and optic nerve function. These studies help to determine whether there has been an otherwise silent demyelinating lesion to the CNS. Among the evoked potential studies, the highest yield for diagnosis in people with probable MS are the somato-sensory EPs, followed by the visual EPs. As a group, their use has declined due to the advent of MRI as a tool for diagnosis.

Table 2 CSF Disease Markers in MS

Marker	Description
Oligoclonal bands (OGCB)	OGCB are produced by the overrepresentation of particular antibodies. They are *typical* of the CSF of MS patients, but not *exclusive* to it.
Intrathecal immunoglobulin production (IgG, IgM)	Immunoglobulins are produced by plasma cells and are integral in adaptive immune responses. Polyclonal increases of IgG occur in chronic infection and inflammation.
Myelin basic protein (MBP)	A major component of myelin, MBP is increased in the CSF of some, but not all, MS patients following a demyelinating episode.

NEUROPSYCHOLOGICAL/CLINICAL PRESENTATION

MS is a chronic recurrent inflammatory neurological disease in which immune-mediated events contribute to subsequent neurologic impairment and disability. It is a complex and frequently active disease process that involves diverse pathological and clinical features. Based mostly in studies of the natural history of the MS disease, some clinical subtypes have been defined (Table 3). It is known that the majority of individuals followed in natural history studies develop progressive disability over long periods of time. Also later stages of the disease are marked by reduced relapses but continued worsening and progressive deterioration.

Table 3 Clinical Subtypes of Multiple Sclerosis (MS)

Relapsing-remitting MS	This is the major MS subtype. Approximately 66–85% of patients with a diagnosis of MS start out with relapsing MS, but after 10 years, only half are still relapsing. Relapsing MS patients show a high rate of inflammatory lesion activity (gadolinium-enhancing lesions).
Primary progressive MS	This subtype accounts for 10–15% of MS. Patients show gradual worsening from onset, without disease attacks. These patients tend to be older and often present with a spinal cord dysfunction without obvious brain involvement. This subtype is the least likely to show inflammatory lesion activity on MRI (gadolinium-enhancing). Unlike the other subtypes of MS, men are as likely as women to develop primary progressive MS.
Progressive relapsing MS	This subtype accounts for about 5% of MS. Patients show slow worsening from onset, with superimposed attacks. Recent studies suggest these patients are similar to primary progressive patients.
Secondary progressive MS	This is the major progressive subtype and accounts for approximately 30% of MS. About half of the relapsing MS patients usually transition to secondary progressive disease. They show gradual worsening, with or without superimposed relapses. Natural history studies of untreated relapsing MS indicate 50% of patients will be secondary progressive at 10 years and almost 90% by 25 years. This form of MS shows a lower rate of inflammatory lesion activity than relapsing MS, yet the total burden of disease continues to increase. This most likely reflects ongoing axonal loss.

The clinical presentation and course of MS is variable and sometimes unpredictable as it is influenced by brain pathology and the individual disease course in each patient. Similarly, the neuropsychological symptoms can vary within subtypes at different stages of the disease (Patti, Amato, Trojano, Lijoi, & Bastianello, 2008). Although MS subtypes have been identified based on severity and progression, the clinical neuropsychological presentation within subtypes is quite unpredictable and overlaps with motor/neuromuscular and affective domains. However, despite the difficulties in establishing a neuropsychological profile in MS, some variables including the area of the lesions, progression of disease, number of years from initial diagnosis, mood/depression, and fatigue mediate the neuropsychological symptoms in each patient (Amato, Zipoli, & Portaccio, 2006). Recently, some researchers have established that neuropsychological symptoms are one of the most disabling yet poorly understood and measured features of the disease and have been documented in 40% to 60% of the patients (Huijbregts et al., 2004; Rao et al., 1991). Also, these symptoms can predict performance on simple and complex activities of daily living (Gaudino et al., 2006) needed for occupational tasks and independent living.

Comprehensive neuropsychological assessments evidence that in MS these symptoms may be broadly subdivided into two broad categories that include mood and cognitive functioning difficulties (Feinstein, 2004). Although they vary in severity, cognitive symptoms in MS involve deficits on visuospatial skills, memory, speed of processing, visuospatial abilities, sensorimotor functions, executive functions, concept formation, abstract reasoning, and verbal fluency (Schulthesis, Garay, & DeLuca, 2001). Cognitive symptoms have been found to be a good predictor of distress and disability (Rao et al., 1991), as well as occupational, social, and overall impairment (Bagert, Camplair, & Bourdette, 2002; Rao et al., 1991). Although no consensus has been established neuropsychological impairment in MS seems to increase and overlap with physical disability and progression (Bobholz & Rao, 2003).

Cognitive deficiencies tend to be more prevalent in the later stages (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1998; Heaton, Nelson, Thompson, Burks, & Franklin, 1985), although in some cases they may be detectable at an early phase of the disease (Bagert et al., 2002; Grant, McDonald, Trimble, Smith, & Reed, 1984; Lyon-Caen et al., 1986). Earlier symptoms can involve information processing speed and verbal fluency (Arango-Laspirilla, DeLuca, & Chiaravalloti, 2007). The later symptoms may involve deficits in memory, conceptual/abstract reasoning, attention, moderate to severe decrease in the speed

of information processing, and visuospatial functions (Bagert et al., 2002; Rao, 1986; Ron, Callanan, & Warrington, 1991). A recent study with 416 relapsing–remitting patients found that processing speed seems to be the most significant cognitive symptom in RRMS (Nocentini et al., 2006).

Sensorimotor Functions

As discussed earlier, MS primary symptoms involve sensorimotor dysfunction; however, presentations are different and therefore the severity and the pattern of dysfunction may vary in each case. Visual impairment is a cardinal symptom in optic neuritis. Motor output sequences become slower due to demyelization and the degeneration characteristic of MS. In MS, motor impairment can be evident with tests that involve different aspects of gross and fine motor output, motor speed, and perceptual skills. In fact, many of the most current cognitive batteries recommended for MS have tried to control for sensory motor effects like the Paced Auditory Serial Addition Test (PASAT), the oral Symbol Digit Modalities Test (SDMT), the Rao's Brief Repeatable Battery (BRB), and the Stroop Color Word Task in order to assess more complex cognitive skills.

Visuospatial Skills, Visuocostructive Abilities

Visuospatial and visuoperceptual abilities are complex procedures that include sensorimotor, executive, and perceptual abilities. In general, these appear to be impaired in approximately 20% of patients with MS (Prakash, Snoook, Lewis, Motl, & Kramer, 2008). Taking into consideration that patients might experience significant visuospatial, visuoperceptual, and visuoconstructive abilities, cognitive evaluation should be specific and take into account the perceptual deficits that might interfere with other cognitive domains. The Benton Visual Orientation Tests are helpful in determining visuospatial and visuoperceptual difficulties. Clinical treatment and recommendations for MS patients should be supported with a minimal screening of visual functions since the quality of life and safety of a patient might change (e.g., driving) as a direct consequence of visuospatial impairment.

Memory

Performance in memory measures of MS might be in part influenced by the attention and psychomotor speed difficulties that these patients experience; therefore, measures used to evaluate different aspects of a patient's memory should control for the above, for example, visuoperceptual deficits and processing speed. Short-term memory and working memory (WM) studies in MS have found that arithmetic seems to be more impaired in patients with MS suggesting that WM deficits tend to be more pervasive as they involve processing simultaneous information. In addition to evaluating processing speed, the PASAT evaluates verbal WM. Consistently, studies have found that 20% to 25% of MS patients tend to present significant impairment on the PASAT as compared with controls (Demaree, DeLuca, Gaudino, & Diamond, 1999; Rao, Leo, Bernardin, & Unverzagt, 1991). Other studies using newer experimental procedures such as the N-back Test that RRMS patients present impairment relative to complexity after taking simple motor speed into account (Parmenter, Shucard, Benedict, & Shucard, 2006; Parmenter, Shucard, & Shucard, 2007). WM deficits seem to be directly related to the course and severity of the disease and primary progressive patients seemed to be more impaired in WM (Zakanis, 2000). Similarly, De Luca establishes that the fundamental difficulties in WM are directly related to processing speed. (DeLuca et al., 2004).

Long-term memory performance seems to be associated with WM and processing speed; however, MS patients tend to maintain an adequate capacity to learn new information (DeLuca, Barbieri-Berger, & Johnson, 1994) and learning trials of lists evidence that the learning slope remains intact (DeLuca et al., 2004; Prakash et al., 2008). Long-term declarative memory impairment also seems to be mediated by impairment in retrieval of information, whereas storage and consolidation of memory seem to be relatively preserved where recognition trials seem to improve retrieval and represent the learning and consolidation processes (Randolph, Arnett, & Higginson, 2001). Difficulties in long-term memory in MS seem to be related to poor encoding, semantic clustering, reduction of semantic categorization, and interference (Arnett et al., 1997).

Speed of Processing

Processing speed deficits seem to be the most evident and fundamental deficit in MS (DeLuca et al., 2004; Parmenter et al., 2007). Due to the white matter abnormalities of MS and lack of myelin in nerve conduction, processing speed difficulties are identified in many patients with MS (DeLuca et al., 2004). However, the differences in the Trail Making Test are not that evident (Arnett et al., 1997). Understanding the challenges of conducting assessments accurately, Rao (1990) developed the PASAT to specifically evaluate the processing capacities without the visual and motor interference that might be present in the disease. The PASAT has been translated and adapted to many languages and has become part of the official National Multiple Sclerosis Society recommended cognitive screening.

Executive Functions

The Wisconsin Card Sorting Test (WCST) and the Halstead Category Test (HCT) are the most commonly used assessments for evaluating executive functions in terms of planning, flexibility, and inhibition. On both measures, MS patients seem to present moderate to severe deficits that are in part mediated by processing speed difficulties (Arnett et al., 1997). Executive deficits in MS have been associated with depressed mood. However, it seems that nonspeeded tax index using the Tower of London (TOL) (as measured by the TOL-moves per trial) indicated a deficient nonspeeded central executive skill secondary to the slow information processing deficits (Arnett, Higginson, & Randolph, 2001). Also, deficits in executive functions may be evident in clinical observations and everyday quality of life questionnaires.

Language/Verbal Fluency

Studies of neuropsychological measures of language functioning in MS have found that verbal fluency tends to be affected even at early stages of the disease (Beatty, 2002; Prakash et al., 2008). In contrast, confrontational naming seems to be more preserved (Vlaar & Wade, 2003). However, in the areas of verbal comprehension and overall verbal IQ (Wechsler Adult Intelligence Scale [WAIS]), MS patients have exhibited mild difficulties (Matotek, Saling, Gates, & Sedal, 2001; Prakash et al., 2008), although deficits seem to be associated with time and severity of the disease (Drake, Allegri, & Carrá, 2002).

Intellectual Abilities

As a consequence of sensory motor difficulties observed in MS, general intelligence measures like the Wechsler's Intelligence Scale reveal that MS patients tend to have difficulties in performance subtests and perceptual reasoning indexes (Prakash et al., 2008). However, when comparing performance within the MS samples, performance IQ seems to be more impaired than verbal IQ even in patients with no physical disability as measured with Expanded Disability Status Scale (EDSS) (Prakash et al., 2008). Nonetheless, intelligence as a general measure depends on lower hierarchy functions like speed of processing, sensory, and motor functions, which are all consistently negatively affected in patients with MS. In conclusion, neuropsychological assessments adapted for MS should always be considered as alternate and supplemental instruments rather than the traditional batteries of intelligence.

Affective and Emotional Symptoms

Cognitive difficulties can be confounded by the emotional symptoms and psychiatric manifestations that accompany this disorder. In contrast, some researchers support that the cognitive symptoms observed in MS patients lack motor and physical impairment, whereas others observe a connection between physical disability and cognitive symptoms (Van Den Burg et al., 1987).

The emotional disturbances most commonly associated with MS are depression and anxiety (Randolph, Arnett, & Freeske, 2004). However, findings support that depression is the most prominent emotional disturbance identified in MS (Arnett, 2005). Proper identification of depression in MS might be difficult since the cardinal symptoms of MS are very similar and overlap with the fiscal disability. Further, in some tests such as the Beck Depression Inventory, many items such as the ones involving fatigue could be specific symptoms more associated with MS than symptoms of depression. For example, concentration difficulties, psychomotor retardation, and sexual dysfunction in MS patients can be considered symptoms of depression, but they can also be a pathophysiological manifestation of MS (Voss et al., 2001). In 2001, Voss and colleagues discovered that physical disability and fatigue were indirectly predictive of depressed mood via recreational functioning. However, fatigue was directly related to depressed mood in MS. Another study conducted by Arnett and Randolph in 2006 using the Beck Depression Inventory and the Chicago Multiscale Depression Inventory (CMDI) Evaluative Symptoms and the CMDI-Vegetative Symptoms assessed different symptom clusters of mood (negative evaluative and neurovegetative) and its relation to active coping strategies in MS. Interestingly, they found that although the lifetime prevalence of depression seems to be very high, the mood symptoms tend to be more variable over long periods of time than negative or neurovegetative symptoms, and increased use of active coping strategies tended to decrease depressed mood longitudinally (Arnett & Randolph, 2006). Also, they found that MS patients that use Beta interferon tended to present a higher risk for depression. Other studies of MS and depression have focused on exploring what affective and cognitive factors contribute to the presence of depression symptoms. One of these studies found that objective executive difficulties contributed to depression; however, the authors found depressive attitudes and depression treatment also mediated memory complaints (Memory Functioning Questionnaire [MFQ]). The authors concluded that interventions for depression might improve the patient's self-perceptions and quality of life (Randolph et al., 2004).

Fatigue in MS

In MS patients experience unpredictable fluctuations in their energy and mood that result in physical, psychological, and social deficits. Some research has shown that in MS patients, fatigue was a direct effect of a patient's mood state (Voss et al., 2001). Nevertheless, fatigue in MS can be distinguished from fatigue related to traditional symptoms of depression, based on the fact that fatigue in MS is aggravated by heat, is often alleviated by sleep, and lasts for only a few hours compared with the more persistent fatigue associated with depression (Patten & Metz, 2002). Alternative treatments such as yoga have been reported to improve fatigue symptoms; other pharmacological treatments such as modafinil have presented mixed results. Assessing each patient's individual symptoms of fatigue is crucial in determining best treatment options.

DIAGNOSIS

Current diagnosis of MS requires a more specific set of criteria requiring the evidence of recurrent neurological deficits, which typically consist of sensory disturbances, optic neuritis, diplopia, limb weakness, clumsiness, and gait ataxia. The diagnosis of MS since its original descriptions has been one based mostly on history and clinical findings. Recurrent neurological deficits disseminated in space and time are basic requirements for diagnosis. These deficits can include sensory disturbances, optic neuritis, diplopia, limb weakness, clumsiness, and gait ataxia. Different diagnostic criteria have been developed over time, and currently MRI has been recognized as an essential tool to exclude other possible diagnosis, to give uniformity to a disease that has such variable presentations, and to account that there was progression of disease. In 2001, the McDonald International Panel proposed a new diagnostic scheme for diagnosis, which replaced previous criteria, incorporated MRI findings (Table 4)

and paraclinical studies such as CSF and visual EPs with neurological history and examination. These criteria were revised in 2005. Diagnosis of MS according to McDonald criteria requires either clinical or radiographic evidence of one or more “attacks” with dissemination in time in conjunction with objective evidence by clinical examination or MRI of lesions with dissemination in space. Revised MRI criteria for dissemination in time requires either gadolinium-enhancing lesion(s) at least 3 months after onset of a clinical event but not corresponding to the site associated with the event or detection at any time of a new T2 lesion that was not present on a reference scan performed at least 30 days after an initial event. Despite evolving MS diagnostic criteria, for an accurate diagnosis, there is no substitute for careful consideration of the patient's history, neurological examination, imaging results, laboratory tests, CSF analysis, EPs, and testing that excludes other possible diagnosis.

Clinically Isolated Syndrome

This refers to patients who present with an isolated CNS syndrome (optic neuritis, incomplete transverse myelitis, brainstem or cerebellar lesion), which is often the first MS attack. Clinical, MRI, and CSF studies indicate that such patients with normal brain MRI and CSF have a low risk of developing MS. In contrast, those with abnormal MRI have a high risk of developing MS (Tintoré et al., 2003).

Table 4 MRI Evidence of Dissemination in Space by McDonald Criteria

3 of the following (one spinal cord lesion can be substituted for one brain lesion):
- One gadolinium-enhancing lesion or 9 T2 hyperintense lesions
- One or more juxtacortical lesions
- One or more infratentorial lesions
- Three or more periventricular lesions

Common	*Uncommon*
Sensory problems (numbness or tingling of a body part)	Bladder problems
Weakness	Bowel problems
Difficulty walking	Sexual dysfunction
Monocular decreased vision	Cognitive difficulties
Poor coordination	Pain

Brain Lesions	*Spinal Cord Lesions*
High signal on T2-weighted and FLAIR MRI sequences	1 or 2 vertebral segments in length
When actively inflamed, often enhanced with gadolinium contrast	Generally incomplete cross-sectional involvement (dorsolateral common)
Position abutting ventricles (often perpendicular)	Less likely to enhance with gadolinium contrast
Juxtacortical position (gray–white junction)	No cord swelling
Involvement of brainstem, cerebellum, or corpus callosum	Better seen with STIR MRI sequences

Disease Categories	*Examples*
Vascular diseases	Vasculitis, antiphospholipid antibody syndrome, CADASIL, cerebrovascular disease, Susac syndrome
Infectious diseases	Bacterial (Lyme disease, syphilis, Whipple’s disease), viral (HIV infection, human T-lymphotrophic virus Type-1 infection, herpes viruses, progressive multifocal leukoencephalopathy, JC virus)
Neoplastic diseases	Primary brain tumor (i.e., CNS lymphoma), metastatic tumors, paraneoplastic syndromes
Structural or compressive conditions	Cervical spondylosis, degenerative disc disease, Chiari malformation, dural arteriovenous fistulas, syrinx
Inflammatory diseases	Collagen vascular diseases (SLE, Sjogren’s syndrome), neurosarcoidosis, Bechet’s disease
Genetic conditions	Leukodystrophies (adrenoleukodystrophy, adrenomyeloneuropathy), lysosomal storage diseases, Fabry’s disease, mitochondrial diseases
Metabolic diseases	Vitamin B12 deficiency, acquired copper deficiency, folate deficiency, hyperhomocysteinemia, vitamin E deficiency
Psychogenic conditions	Conversion disorder, depression, anxiety

In patients with CIS suggestive of demyelination, evidence for dissemination in time and space could be provided by MRI alone. Dissemination in space can be identified by meeting three of four MRI criteria, or, alternatively, by showing at least two lesions plus the presence of OGCB (or elevated IgG index) in CSF. In a multicenter study, it was shown that if Barkhof/Tintoré criteria are fulfilled the likelihood for conversion to clinically definite MS is much higher and the time much shorter than if criteria are not fulfilled (Korteweg et al., 2006).

Early, routine, and yearly assessment of neurological symptoms in MS patients is a critical aspect required in the careful monitoring of a patient's disease progression, response to treatment, and overall quality of life. Despite the evidence that cognitive and emotional symptoms have a significant impact on the patient's quality of life, a study revealed that in 2002, MS clinics and neurological practices did not routinely conduct neuropsychological assessments. This may have been attributed to a lack of consensus in the field about the right way to evaluate MS (Benedict et al., 2002). As a result of the discrepancy, a group of neurologists and neuropsychologists from the United States, Canada, the United Kingdom, and Australia met together and agreed that the new standard for diagnosing MS would require a minimal neuropsychological assessment. These experts developed the Minimal Assessment of Cognitive Function in MS (MACFIMS). The MACFIMS is a 90 min battery composed of seven neuropsychological tests that evaluate the domains of processing speed, WM, learning and memory, executive function, visuospatial processing, word retrieval, and provides recommendations for evaluation of sensorimotor functions, fatigue, and depression (Benedict et al., 2002). Some of the tests that have proven to be effective with MS patients are Rao's BRB, MS Neuropsychological Screening Questionnaire, PASAT, SMDT (Smith, 1982), California Verbal Learning Test, and the Brief Visuospatial Memory Test.

TREATMENT

Today there are many innovative disease-modifying treatments for MS that aim to decrease the possibility of new clinical relapses or slow the progression of the disease by MRI. The first method of treatment is through interferons, which are naturally occurring antiviral proteins. Interferon beta-1a low dose (Avonex) and high dose (Rebif) as well as interferon beta-1b

(Betaseron) have been shown to alter the natural history of RRMS. The interferon treatments have been shown to decrease the number of exacerbations and may slow the progression of the physical disability. These medications vary in their dose and frequency and are thought to work by modifying the effects of endogenous interferons on the immune system. Other treatment available is glatiramer acetate (Copaxone), which consists of a mixture of peptide fragments thought to act as a decoy for the immune system to spare myelin from further attack. All of the above treatments are injected subcutaneously with the exception of interferon beta-1a low dose which is injected intramuscularly. Current therapeutic treatments have been shown to work best in the more active inflammatory phases early in the disease. Natalizumab is a monoclonal antibody given intravenously once per month for patients who have been on the above medications with poor response or have eventually failed treatment. Chemotherapeutic agents such as mitoxantrone are being used as an alternative form of treatment for more aggressive progression like in the case of secondary progressive MS. The chemotherapeutic form of treatment is more a last resort because of the amount of undesirable side effects it causes. Newer therapies are currently under study including oral medications to avoid relapses. Unfortunately, none of the existing pharmaceutical interventions “cure” the disease. In addition, the markers for success are typically MRI lesions, which, as indicated earlier, do not appear to have a strong correlation with functional and cognitive limitations.

For acute exacerbations, intravenous corticosteroids are the treatment of choice that is frequently used for the purpose of hastening recovery in a patient who has already had a relapse. These anti-inflammatory agents suppress cell migration into the CNS, reducing inflammation around active plaques. They are usually administered for 3–5 days and then rapidly tapered down or discontinued. Less conventional therapies that can be used at times, in more aggressive cases, are intravenous immunoglobulin or plasma exchange. Symptomatic therapy includes treatment for associated spasticity, pain, bladder dysfunction, tremors, or fatigue. It is very important for the clinician to assess symptoms that can be secondary to fatigue, heat, lack of rest, or inadequate diet since these can mimic an acute relapse associated with a worsening of previous deficits. The addition of nonmedical interventions may be as critical, if not more, than the previously discussed interventions. These would include but not be limited to temperature regulation, fatigue control, massage, controlled exercise, vocational intervention, and psychotherapy.

The course of this disease is quite variable in each patient. Relapses may have measurable and lasting impact causing disability at a later time. Subtle clinical symptoms can be related to active inflammatory activity that can go unnoticed in the absence of careful evaluation. It is thought that roughly 15% of MS patients will never have a relapse and that most MS patients will eventually develop the secondary progressive form of MS. Factors that have been associated with poorer prognosis are frequent relapses in the first 2 years, primary progressive onset, male sex, the presence of multiple MRI lesions, and early motor or cerebellar findings.

EDSS is the most widely used scale for assessing level of disability in MS patients (Kurtzke, 1983). This rating system is frequently used for classifying and standardizing the condition of people with MS; it is also an important tool in clinical trials (can be used as inclusion/exclusion criteria and to compare results). The score is based on a clinical neurological examination and consists of a number scale from 0 to 10 where the range from 0.0 to 4.5 includes patients who are ambulatory and the range from 5.0 to 9.5 is defined by impairment of ambulation. Although it provides an objective measure, there is an apparent discrepancy between conventional lesions in MRI and clinical disability as measured by this scale (Li et al., 2006) since it places emphasis on the ability to walk and it may not be able to detect the extensive clinical changes that patients can experience.

In general, the course and manifestation of symptoms in MS are quite variable in each patient. Relapses may have measurable and lasting impact causing disability at a later time. Subtle clinical symptoms can be related to active inflammatory activity that can go unnoticed in the absence of careful evaluation. It is thought that roughly 10% of patients have benign MS and that 70% will become secondary progressive.

Bibliography

- Amato, M. P.; Zipoli, V.; Portaccio, E. (2006). Multiple sclerosis related cognitive changes: A review of cross-sectional and longitudinal studies. Journal of Neurology Science, 245, 41-46. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Neurology Science&rft.atitle=Multiple sclerosis related cognitive changes: A review of cross-sectional and longitudinal studies&rft.date=2006&rft.aulast=Amato&rft.aufirst=M. P.&rft.volume=245&rft.spage=41)
- Arango-Laspirilla, J. C.; DeLuca, J.; Chiaravalloti, N. (2007). Neuropsychological profile of multiple sclerosis. Psicothema, 19(1), 1-6. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
profile of multiple sclerosis&rft.date=2007&rft.aulast=Arango-Laspirilla&rft.aufirst=J. C.&rft.volume=19&rft.issue=1&rft.spage=1)
- Arnett, P. A. (2005). Longitudinal consistency of the relationship between depression symptoms and cognitive functioning in multiple sclerosis. Central Nervous System Spectrums, 10(5), 372-382. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Nervous System Spectrums&rft.atitle=Longitudinal consistency of the relationship between depression symptoms and cognitive functioning in multiple sclerosis&rft.date=2005&rft.aulast=Arnett&rft.aufirst=P. A.&rft.volume=10&rft.issue=5&rft.spage=372)

- Arnett, P. A.; Higginson, C. I.; Randolph, J. J. (2001). Depression in multiple sclerosis: Relationship to planning ability. Journal of the International Neuropsychological Society, 7(6), 665-674. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of the International Neuropsychological Society&rft.atitle=Depression in multiple sclerosis: Relationship to planning ability&rft.date=2001&rft.aulast=Arnett&rft.aufirst=P. A.&rft.volume=7&rft.issue=6&rft.spage=665)
- Arnett, P. A.; Higginson, C. I.; Voss, W. D.; Wright, B.; Bender, W. I.; Wurst, J., et al. (1999). Depressed mood in multiple sclerosis: Relationship to capacity demanding memory and attentional functioning. Neuropsychology, 13(3), 434-446. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g mood in multiple sclerosis: Relationship to capacity demanding memory and attentional functioning&rft.date=1999&rft.aulast=Arnett&rft.aufirst=P. A.&rft.volume=13&rft.issue=3&rft.spage=434)
- Arnett, P. A.; Randolph, J. J. (2006). Longitudinal course of depression symptoms in MS. Journal of Neurology, Neurosurgery, & Psychiatry, 77, 606-610. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology, Neurosurgery, %26 Psychiatry&rft.atitle=Longitudinal course of depression symptoms in MS&rft.date=2006&rft.aulast=Arnett&rft.aufirst=P. A.&rft.volume=77&rft.spage=606)
- Arnett, P. A.; Rao, S.; Graffman, J.; Bernardin, L.; Luchetta, T.; Binder, J., et al. (1997). Executive functions in multiple sclerosis: An analysis of temporal ordering, semantic encoding, and planning abilities. Neuropsychology, 11(4), 535-544. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g functions in multiple sclerosis: An analysis of temporal ordering, semantic encoding, and planning abilities&rft.date=1997&rft.aulast=Arnett&rft.aufirst=P. A.&rft.volume=11&rft.issue=4&rft.spage=535)
- Bagert, B.; Camplair, P.; Bourdette, D. (2002). Cognitive dysfunction in multiple sclerosis: Natural history, pathophysiology and management. Central Nervous System Drugs, 16(7), 445-455. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Nervous System Drugs&rft.atitle=Cognitive dysfunction in multiple sclerosis: Natural history, pathophysiology and management&rft.date=2002&rft.aulast=Bagert&rft.aufirst=B.&rft.volume=16&rft.issue=7&rft.spage=445)
- Bakshi, R.; Hutton, G. J.; Miller, J. R.; Radue, E. W. (2004). The use of magnetic resonance imaging in the diagnosis and long-term management of multiple sclerosis. Neurology, 63 (Suppl. 5), S3-S11. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g use of magnetic resonance imaging in the diagnosis and long-term management of multiple sclerosis&rft.date=2004&rft.aulast=Bakshi&rft.aufirst=R.&rft.volume=63&rft.spage=S3)
- Beatty, W. W. (2002). Fluency in multiple sclerosis: Which measure is best? Multiple Sclerosis, 8, 261-264. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Sclerosis&rft.atitle=Fluency in multiple sclerosis: Which measure is best&rft.date=2002&rft.aulast=Beatty&rft.aufirst=W. W.&rft.volume=8&rft.spage=261)
- Beatty, W. W.; Goodkin, D. E.; Monson, N.; Beatty, P. A.; Hertsgaard, D. (1998). Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. Archives of Neurology, 45, 611-619. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology&rft.atitle=Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis&rft.date=1998&rft.aulast=Beatty&rft.aufirst=W. W.&rft.volume=45&rft.spage=611)
- Benedict, R. H.; Fisher, J. S.; Archibald, C. J.; Arnett, P. A.; Beatty, W. W.; Bobholz, J., et al. (2002). Minimal neuropsychological assessment in multiple sclerosis patients: A consensus approach. Clinical Neuropsychology, 16(3), 381-397. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Neuropsychology&rft.atitle=Minimal neuropsychological assessment in multiple sclerosis patients: A consensus approach&rft.date=2002&rft.aulast=Benedict&rft.aufirst=R. H.&rft.volume=16&rft.issue=3&rft.spage=381)
- Benedict, R. H.; Weinstock-Guttman, B.; Fishman, I.; Sharma, J.; Tjoa, C. W. (2004). Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measure atrophy and lesion burden. Archives of Neurology, 61(2), 226-230. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology&rft.atitle=Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measure atrophy and lesion burden&rft.date=2004&rft.aulast=Benedict&rft.aufirst=R. H.&rft.volume=61&rft.issue=2&rft.spage=226)
- Bobholz, J. A.; Rao, S. M. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. Current

Opinion in Neurology, 16, 283-288. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Opinion in Neurology&rft.atitle=Cognitive dysfunction in multiple sclerosis: A review of recent developments&rft.date=2003&rft.aulast=Bobholz&rft.aufirst=J. A.&rft.volume=16&rft.spage=283)

- Cristodoulou, C.; Krupp, L. B.; Liang, Z.; Huang, W.; Melville, P.; Roque, C., et al. (2003). Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. Neurology, 60(11), 1793-1798. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
performance and MR markers of cerebral injury in cognitively impaired MS patients&rft.date=2003&rft.aulast=Cristodoulou&rft.aufirst=C.&rft.volume=60&rft.issue=11&rft.spage=1793)
- DeLuca, J.; Barbieri-Berger, S.; Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. Journal of Clinical & Experimental Neuropsychology, 16(2), 183-189. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Clinical %26 Experimental Neuropsychology&rft.atitle=The nature of memory impairments in multiple sclerosis: acquisition versus retrieval&rft.date=1994&rft.aulast=DeLuca&rft.aufirst=J.&rft.volume=16&rft.issue=2&rft.spage=183)
- DeLuca, J.; Christodoulou, C.; Diamond, B. J.; Rosenstein, E. D.; Kramer, N.; Ricker, J. H., et al. (2004). The nature of memory impairment in chronic fatigue syndrome. Rehabilitation Psychology, 49(1), 62-70. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Psychology&rft.atitle=The nature of memory impairment in chronic fatigue syndrome&rft.date=2004&rft.aulast=DeLuca&rft.aufirst=J.&rft.volume=49&rft.issue=1&rft.spage=62)
- De Jager, P. L.; Simon, K. C.; Munger, K. L.; Rioux, J. D.; Hafler, D. A.; Ascherio, A. (2008). Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis. Neurology, 70(13, Pt. 2), 1113-1118. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis&rft.date=2008&rft.aulast=De Jager&rft.aufirst=P. L.&rft.volume=70&rft.spage=1113)
- Demaree, H. A.; DeLuca, J.; Gaudino, E. A.; Diamond, B. J. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. Journal of Neurology, Neurosurgery & Psychiatry, 67(5), 661-663. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Neurology, Neurosurgery %26 Psychiatry&rft.atitle=Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation&rft.date=1999&rft.aulast=Demaree&rft.aufirst=H. A.&rft.volume=67&rft.issue=5&rft.spage=661)
- Dhib-Jalbut, S. (2007). Pathogenesis of myelin/oligodendrocyte damage in multiple sclerosis. Neurology, 68(22, Suppl. 3), S13-S21; discussion S43-S54. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of myelin/oligodendrocyte damage in multiple sclerosis&rft.date=2007&rft.aulast=Dhib-Jalbut&rft.aufirst=S.&rft.volume=68&rft.spage=S13)
- Drake, M.; Allegri, R. F.; Carrá, A. (2002). Alteraciones del Lenguaje en Pacientes con Esclerosis Múltilple. Neurología, 17(1), 12-16. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
del Lenguaje en Pacientes con Esclerosis Múltilple&rft.date=2002&rft.aulast=Drake&rft.aufirst=M.&rft.volume=17&rft.issue=1&rft.spage=12)
- Dutta, R.; Trapp, B. D. (2007). Pathogenesis of axonal and neuronal damage in multiple sclerosis. Neurology, 68(22, Suppl. 3), S22-S31; discussion S43-S54. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of axonal and neuronal damage in multiple sclerosis&rft.date=2007&rft.aulast=Dutta&rft.aufirst=R.&rft.volume=68&rft.spage=S22)
- Ebers, G. C. (2008). Environmental factors and multiple sclerosis. Lancet Neurology, 7(3), 268-277. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Neurology&rft.atitle=Environmental factors and multiple sclerosis&rft.date=2008&rft.aulast=Ebers&rft.aufirst=G. C.&rft.volume=7&rft.issue=3&rft.spage=268)
- Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. Canadian Journal of Psychiatry, 49(3), 157-163. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Journal of Psychiatry&rft.atitle=The neuropsychiatry of multiple sclerosis&rft.date=2004&rft.aulast=Feinstein&rft.aufirst=A.&rft.volume=49&rft.issue=3&rft.spage=157)
- Fillipi, M.; Bozzali, M.; Rovaris, M.; Gonen, O.; Kesavadas, C.; Ghezzi, A., et al. (2003). Evidence for widespread axonal

damage at the earliest clinical stages of multiple sclerosis. Brain, 126, 433-437. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g for widespread axonal damage at the earliest clinical stages of multiple sclerosis&rft.date=2003&rft.aulast=Fillipi&rft.aufirst=M.&rft.volume=126&rft.spage=433)

- Gaudino, E.; DeLuca, J.; Voebel, G.; Goverover, Y.; Moore, N.; Halper, J. (2006). Using the MSFC to predict performance on complex activities of daily living in MS. Paper presented at the Annual Meeting of the International Neuropsychological Society, Boston, MA.2006. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Abook&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.ge the MSFC to predict performance on complex activities of daily living in MS&rft.date=2006&rft.aulast=Gaudino&rft.aufirst=E.&rft.spage=2006)
- Grant, I.; McDonald, W. I.; Trimble, M. R.; Smith, E.; Reed, R. (1984). Deficient learning and memory in early and middle phases of multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry, 47, 250-255. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology, Neurosurgery %26 Psychiatry&rft.atitle=Deficient learning and memory in early and middle phases of multiple sclerosis&rft.date=1984&rft.aulast=Grant&rft.aufirst=I.&rft.volume=47&rft.spage=250)
- Haase, C. G.; Tinnefeld, M.; Lieneman, M.; Ganz, R. E.; Faustmann, P. M. (2003). Depression and cognitive impairment in disability free early multiple sclerosis. Behavioral Neurology, 14, 39-45. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Neurology&rft.atitle=Depression and cognitive impairment in disability free early multiple sclerosis&rft.date=2003&rft.aulast=Haase&rft.aufirst=C. G.&rft.volume=14&rft.spage=39)
- Heaton, R. K.; Nelson, L. M.; Thompson, D. S.; Burks, J. S.; Franklin, G. M. (1985). Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. Journal of Consulting and Clinical Psychology, 53, 103-110. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Consulting and Clinical Psychology&rft.atitle=Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis&rft.date=1985&rft.aulast=Heaton&rft.aufirst=R. K.&rft.volume=53&rft.spage=103)
- Huijbregts, S. C.; Kalkers, N. F.; de Sonneville, L. M.; de Groot, V.; Reuling, I. E.; Polman, C. H. (2004). Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology, 63, 335-339. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g in cognitive impairment of relapsing remitting, secondary, and primary progressive MS&rft.date=2004&rft.aulast=Huijbregts&rft.aufirst=S. C.&rft.volume=63&rft.spage=335)
- Korteweg, T.; Tintoré, M.; Uitdehaag, B.; Rovira, A.; Frederiksen, J.; Miller, D., et al. (2006). MRI criteria for dissemination in space in patients with clinically isolated syndromes: A multicentre follow-up study. Lancet Neurology, 5(3), 211-217. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Neurology&rft.atitle=MRI criteria for dissemination in space in patients with clinically isolated syndromes: A multicentre follow-up study&rft.date=2006&rft.aulast=Korteweg&rft.aufirst=T.&rft.volume=5&rft.issue=3&rft.spage=211)
- Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology, 33(11), 1444-1452. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)&rft.date=1983&rft.aulast=Kurtzke&rft.aufirst=J. F.&rft.volume=33&rft.issue=11&rft.spage=1444)
- Kurtzke, J. F. Wallin, M. T. (2000). Epidemiology. In J. S. Burks; K. P. Johnson (Eds.), Multiple sclerosis: Diagnosis, medical management, and rehabilitation (pp. 49-71). Demos Medical Publishing, Inc New York, NY. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Abook&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.ge sclerosis: Diagnosis, medical management, and rehabilitation&rft.atitle=Epidemiology&rft.date=2000&rft.aulast=Kurtzke&rft.aufirst=J. F.&rft.spage=49)
- Li, D.; Held, U.; Petkau, J.; Daumaer, M.; Barkhof, F.; Fazekas, F., et al. (2006). MRI T2 lesion burden in multiple sclerosis: A plateauing relationship with clinical disability. Neurology, 66(9), 1384-1389. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g T2 lesion burden in multiple sclerosis: A plateauing relationship with clinical disability&rft.date=2006&rft.aulast=Li&rft.aufirst=D.&rft.volume=66&rft.issue=9&rft.spage=1384)
- Lyon-Caen, O.; Jouvent, R.; Hauser, S.; Chaunu, M. P.; Benoit, N.; Widlöcher, D. (1986). Cognitive function in recent-onset demyelinating diseases. Archives of Neurology, 43, 1138-1141. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?

ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Neurology&rft.atitle=Cognitive function in recent-onset demyelinating diseases&rft.date=1986&rft.aulast=Lyon-Caen&rft.aufirst=O.&rft.volume=43&rft.spage=1138)

- MacLean, H.; Freedman, M. (2009). Multiple sclerosis: Following clues from cause to cure. Lancet Neurology, 8(1), 6-8. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Neurology&rft.atitle=Multiple sclerosis: Following clues from cause to cure&rft.date=2009&rft.aulast=MacLean&rft.aufirst=H.&rft.volume=8&rft.issue=1&rft.spage=6)
- Matotek, K.; Saling, M. M.; Gates, P.; Sedal, L. (2001). Subjective complaints, verbal fluency, and working memory in mild multiple sclerosis. Applied Neuropsychology, 8(4), 204-210. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Neuropsychology&rft.atitle=Subjective complaints, verbal fluency, and working memory in mild multiple sclerosis&rft.date=2001&rft.aulast=Matotek&rft.aufirst=K.&rft.volume=8&rft.issue=4&rft.spage=204)
- McDonald, W. I.; Compston, A.; Edan, G. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of Neurology, 50, 121-127. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Neurology&rft.atitle=Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis&rft.date=2001&rft.aulast=McDonald&rft.aufirst=W. I.&rft.volume=50&rft.spage=121)
- Nocentini, U.; Pasqualetti, P.; Bonavita, S.; Buccafusca, M.; DeCaro, M.; Farina, D., et al. (2006). Cognitive dysfunction in patients with relapsing remitting multiple sclerosis. Multiple Sclerosis, 12(1), 77-78. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Sclerosis&rft.atitle=Cognitive dysfunction in patients with relapsing remitting multiple sclerosis&rft.date=2006&rft.aulast=Nocentini&rft.aufirst=U.&rft.volume=12&rft.issue=1&rft.spage=77)
- Ojera, C.; Rovaris, M.; Inanucci, G.; Valasina, P.; Caputo, D.; Cavarretta, R., et al. (2005). Progressive grey matter damage in patients with relapsing remitting multiple sclerosis: A longitudinal diffusion tensor magnetic resonance imaging study. Archives of Neurology, 62(4), 578-584. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Neurology&rft.atitle=Progressive grey matter damage in patients with relapsing remitting multiple sclerosis: A longitudinal diffusion tensor magnetic resonance imaging study&rft.date=2005&rft.aulast=Ojera&rft.aufirst=C.&rft.volume=62&rft.issue=4&rft.spage=578)
- Parmenter, B. A.; Shucard, J. L.; Benedict, R. H.; Shucard, D. W. (2006). Working memory deficits in multiple sclerosis: comparison between the n-back task and the Paced Auditory Serial Addition Test. Journal of the International Neuropsychological Society, 12(5), 677-687. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of the International Neuropsychological Society&rft.atitle=Working memory deficits in multiple sclerosis: comparison between the n-back task and the Paced Auditory Serial Addition Test&rft.date=2006&rft.aulast=Parmenter&rft.aufirst=B. A.&rft.volume=12&rft.issue=5&rft.spage=677)
- Parmenter, B. A.; Shucard, J. L.; Shucard, D. W. (2007). Information processing deficits in multiple sclerosis: A matter of complexity. Journal of the International Neuropsychological Society, 13(3), 417-423. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of the International Neuropsychological Society&rft.atitle=Information processing deficits in multiple sclerosis: A matter of complexity&rft.date=2007&rft.aulast=Parmenter&rft.aufirst=B. A.&rft.volume=13&rft.issue=3&rft.spage=417)
- Patten, S.; Metz, L. (2002). Interferon ß1a and depression in secondary progressive MS: Data from the SPECTRIMS trial. Neurology, 59(5), 744-746. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
ß1a and depression in secondary progressive MS: Data from the SPECTRIMS trial&rft.date=2002&rft.aulast=Patten&rft.aufirst=S.&rft.volume=59&rft.issue=5&rft.spage=744)
- Patti, F.; Amato, M. P.; Trojano, M.; Lijoi, A.; Bastianello, S. (2008). Relationship between cognitive impairment and magnetic resonance imaging parameters in patients with early relapsing remitting multiple sclerosis: Results from the Multicenter COGIMUS 2008 (COGnitionImpairment in Multiple Sclerosis Study). Neurology, 70(Suppl. D1), P04.170. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
between cognitive impairment and magnetic resonance imaging parameters in patients with early relapsing remitting multiple sclerosis: Results from the Multicenter COGIMUS 2008 (COGnitionImpairment in Multiple Sclerosis Study)&rft.date=2008&rft.aulast=Patti&rft.aufirst=F.&rft.volume=70&rft.spage=170)
- Prakash, R.; Snoook, E.; Lewis, J.; Motl, R.; Kramer, A. F. (2008). Cognitive impairments in multiple sclerosis: A meta-

analysis. Multiple Sclerosis, 1(9), 1250-1261. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Sclerosis&rft.atitle=Cognitive impairments in multiple sclerosis: A meta-analysis&rft.date=2008&rft.aulast=Prakash&rft.aufirst=R.&rft.volume=1&rft.issue=9&rft.spage=1250)

- Randolph, J. J.; Arnett, P. A.; Freeske, P. (2004). Metamemory in multiple sclerosis: Exploring affective and executive contributions. Archives of Clinical Neuropsychology, 19(2), 259-279. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Clinical Neuropsychology&rft.atitle=Metamemory in multiple sclerosis: Exploring affective and executive contributions&rft.date=2004&rft.aulast=Randolph&rft.aufirst=J. J.&rft.volume=19&rft.issue=2&rft.spage=259)
- Randolph, J. J.; Arnett, P. A.; Higginson, C. I. (2001). Metamemory and tested cognitive functioning in multiple sclerosis. The Clinical Neuropsychologist, 15(3), 357-368. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Clinical Neuropsychologist&rft.atitle=Metamemory and tested cognitive functioning in multiple sclerosis&rft.date=2001&rft.aulast=Randolph&rft.aufirst=J. J.&rft.volume=15&rft.issue=3&rft.spage=357)
- Rao, S. M. (1986). Neuropsychology of multiple sclerosis: A critical review. Journal of Clinical Experimental Neuropsychology, 8, 503-542. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of Clinical Experimental Neuropsychology&rft.atitle=Neuropsychology of multiple sclerosis: A critical review&rft.date=1986&rft.aulast=Rao&rft.aufirst=S. M.&rft.volume=8&rft.spage=503)
- Rao, S. M. (1990). Cognitive Function Study Group, NMSS. A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. National Multiple Sclerosis Society New York. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Abook&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.ge
manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis&rft.atitle=Cognitive Function Study Group, NMSS&rft.date=1990&rft.aulast=Rao&rft.aufirst=S. M.)
- Rao, S. M.; Leo, G. J.; Bernardin, L.; Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis I: Frequency patterns & prediction. Neurology, 41(5), 685-691. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
dysfunction in multiple sclerosis I: Frequency patterns %26 prediction&rft.date=1991&rft.aulast=Rao&rft.aufirst=S. M.&rft.volume=41&rft.issue=5&rft.spage=685)
- Rao, S.; Leo, G. J.; Ellington, L.; Nauertz, T.; Bernardin, L.; Unverzagt, F. (1991). Cognitive dysfunction on multiple sclerosis II: Impact on employment and social functioning. Neurology, 41(5), 692-696. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
dysfunction on multiple sclerosis II: Impact on employment and social functioning&rft.date=1991&rft.aulast=Rao&rft.aufirst=S.&rft.volume=41&rft.issue=5&rft.spage=692)
- Ron, M. A.; Callanan, M. M.; Warrington, E. K. (1991). Cognitive abnormalities in multiple sclerosis: A psychometric and MRI study. Psychological Medicine, 21, 59-68. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Medicine&rft.atitle=Cognitive abnormalities in multiple sclerosis: A psychometric and MRI study&rft.date=1991&rft.aulast=Ron&rft.aufirst=M. A.&rft.volume=21&rft.spage=59)
- Ross, A. J.; Sachdev, P. (2004). Magnetic resonance spectroscopy in cognitive research. Brain Research Reviews, 44, 83-102. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
Research Reviews&rft.atitle=Magnetic resonance spectroscopy in cognitive research&rft.date=2004&rft.aulast=Ross&rft.aufirst=A. J.&rft.volume=44&rft.spage=83)
- Rovaris, M.; Inannucci, G.; Falautano, M.; Possa, F.; Martinelli, V.; Comi, G.; Fillipi, M. (2002). Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. Journal of the Neurological Sciences, 195(2), 103-109. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
of the Neurological Sciences&rft.atitle=Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging&rft.date=2002&rft.aulast=Rovaris&rft.aufirst=M.&rft.volume=195&rft.issue=2&rft.spage=103)
- Schulthesis, M. T.; Garay, E.; DeLuca, J. (2001). The influence of cognitive impairment on driving performance in multiple sclerosis. Neurology, 56, 1089-1094. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
influence of cognitive impairment on driving performance in multiple sclerosis&rft.date=2001&rft.aulast=Schulthesis&rft.aufirst=M. T.&rft.volume=56&rft.spage=1089)

- Smith, A. (1982). The symbol digit modalities test manual: Revised. Western Psychological Services Los Angeles. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Abook&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.ge symbol digit modalities test manual: Revised&rft.date=1982&rft.aulast=Smith&rft.aufirst=A.)
- Stanley, J. A. (2002). In vivo magnetic resonance spectroscopy and its implications to neuropsychiatric disorder. Canadian Journal of Psychiatry, 47, 315-326. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Journal of Psychiatry&rft.atitle=In vivo magnetic resonance spectroscopy and its implications to neuropsychiatric disorder&rft.date=2002&rft.aulast=Stanley&rft.aufirst=J. A.&rft.volume=47&rft.spage=315)
- Thrower, B. W. (2007). Clinically isolated syndromes: Predicting and delaying multiple sclerosis. Neurology, 68(24, Suppl. 4), S12-S15. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g isolated syndromes: Predicting and delaying multiple sclerosis&rft.date=2007&rft.aulast=Thrower&rft.aufirst=B. W.&rft.volume=68&rft.spage=S12)
- Tintoré, M.; Rovira, A.; Río, M.; Nos, C.; Grivé, E.; Sastre-Garriga, J., et al. (2003). New diagnostic criteria for multiple sclerosis: Application in first demyelinating episode. Neurology, 60(1), 27-30. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g diagnostic criteria for multiple sclerosis: Application in first demyelinating episode&rft.date=2003&rft.aulast=Tintoré&rft.aufirst=M.&rft.volume=60&rft.issue=1&rft.spage=27)
- Tong, B.; Yip, J.; Mc Lee, T.; Li, L. (2002). Frontal fluency and memory functioning among multiple sclerosis patients in Hong Kong. Brain Injury, 16(11), 987-995. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Injury&rft.atitle=Frontal fluency and memory functioning among multiple sclerosis patients in Hong Kong&rft.date=2002&rft.aulast=Tong&rft.aufirst=B.&rft.volume=16&rft.issue=11&rft.spage=987)
- Tortorella, P.; Rocca, M. A.; Mezzapesa, D.; Ghezzi, A.; Lamanthia, L.; Comi, G., et al. (2006). MRI quantification of gray and white matter damage in patients with early onset multiple sclerosis. Journal of Neurology, 253(7), 903-907. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology&rft.atitle=MRI quantification of gray and white matter damage in patients with early onset multiple sclerosis&rft.date=2006&rft.aulast=Tortorella&rft.aufirst=P.&rft.volume=253&rft.issue=7&rft.spage=903)
- Van den Burg, W.; van Zomeren, A. H.; Minderhoud, J. M.; Prange, A. J.; Meijer, N. S. (1987). Cognitive impairment in patients with multiple sclerosis and mild physical disability. Archives of Neurology, 44, 49-501. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Neurology&rft.atitle=Cognitive impairment in patients with multiple sclerosis and mild physical disability&rft.date=1987&rft.aulast=Van den Burg&rft.aufirst=W.&rft.volume=44&rft.spage=49)
- Vlaar, A. M.; Wade, D. T. (2003). Verbal fluency assessment of patients with multiple sclerosis: Test-retest and inter-observer reliability. Clinical Rehabilitation, 17, 756-764. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g Rehabilitation&rft.atitle=Verbal fluency assessment of patients with multiple sclerosis: Test-retest and inter-observer reliability&rft.date=2003&rft.aulast=Vlaar&rft.aufirst=A. M.&rft.volume=17&rft.spage=756)
- Voss, W. D.; Arnett, P. A.; Higginson, C. I.; Randolph, J. J.; Campos, M. D.; Dyck, D. G. (2001). Contributing factors to depressed mood in multiple sclerosis. Archives of Clinical Neuropsychology, 17, 113-115. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Clinical Neuropsychology&rft.atitle=Contributing factors to depressed mood in multiple sclerosis&rft.date=2001&rft.aulast=Voss&rft.aufirst=W. D.&rft.volume=17&rft.spage=113)
- Vrenken, H.; Pouwels, P. J.; Geurts, J. J.; Knol, D. L.; Polman, C. H.; Barkhof, F., et al. (2006). Altered diffusion tensor in multiple sclerosis normal-appearing brain tissue: Cortical diffusion changes seem related to clinical deterioration. Journal of Magnetic Resonance Imaging, 23(5), 628-636. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Magnetic Resonance Imaging&rft.atitle=Altered diffusion tensor in multiple sclerosis normal-appearing brain tissue: Cortical diffusion changes seem related to clinical deterioration&rft.date=2006&rft.aulast=Vrenken&rft.aufirst=H.&rft.volume=23&rft.issue=5&rft.spage=628)
- Zakanis, K. K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. Archives of Clinical Neuropsychology, 15(2), 115-136. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.g of Clinical Neuropsychology&rft.atitle=Distinct neurocognitive profiles in multiple sclerosis subtypes&rft.date=2000&rft.aulast=Zakanis&rft.aufirst=K. K.&rft.volume=15&rft.issue=2&rft.spage=115)

- Zivadinoff, R.; Bakshi, R. (2004). Role of MRI in multiple sclerosis: Inflammation and lesions. Frontiers in Bioscience, 9, 665-683. Check for Full Text (http://rf2tt2th6w.search.serialssolutions.com/?ctx_ver=Z39.88-2004&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rfr_id=info%3Asid%2Fcredoreference:credoreference&rft.
in Bioscience&rft.atitle=Role of MRI in multiple sclerosis: Inflammation and lesions&rft.date=2004&rft.aulast=Zivadinoff&rft.aufirst=R.&rft.volume=9&rft.spage=665)

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1
Diffusion with tissue integrity in a microscopic scale.

2
Diffusion anisotropy, associated with restricted diffusion.

3
DTI, using directionally selective diffusion measurements, is used to determine the degree of anisotropy in the diffusion of water.