

# Cognitive Disturbance among Patients with Multiple Sclerosis: Systematic Review

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**Abstract:** Multiple sclerosis (MS) is a progressive disease, described by the presence of lesions in brain and spinal cord memory definition concerns to the acquisition operations (as a synonym of learning), formation, conservation and evocation of informations. Although there are various systems to classify memory, within this article, we will emphasize those most frequently investigated in MS patients. The purpose of this systematic review is to present the results of prospective and retrospective studies on cognitive alterations in MS patients. Also to highlight the relationship between MS and cognitive impairment and its risk factors. We conducted systematic search for published studies through electronic bibliographic databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine Database, and PsycInfo in September, 2016. We concluded that there is consensus on cognitive impairment of multiple sclerosis patients, especially on memory, speed processing, executive function, attention and concentration domains.

**Keywords:** Cognitive Disturbance, Multiple sclerosis.

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## 1. INTRODUCTION

Multiple sclerosis (MS) is a progressive disease, described by the presence of lesions in brain and spinal cord<sup>1</sup> and one of the most common central nervous system (CNS) disease of young adults especially females<sup>2</sup>. These plaques have a demyelinating character associated with axonal loss<sup>1,2</sup>. In early phase of the MS, inflammatory process seems to be the background of neurons degeneration, but, lately in disease evolution, there is a predominance of degenerative process other than inflammatory process<sup>2</sup>.

MS occurs in females more frequently than it does in males; ratios of incidence range from 2:1 to 3:1, depending on the geographical region. Despite the elevated frequency in women, studies have shown that disease severity is typically higher and progression more rapid in men compared to women. Additionally, the morbidity and severity of cognitive deficits are higher in males' patients<sup>3</sup>.

Although MS disease incidence is highest in populations from the northern United States, northern Europe, Canada, New Zealand, and southern Australia,<sup>4</sup> people from all countries and of all races have been diagnosed with the disease. Race plays a role in disease pathogenesis and severity. For example, Caucasians have delayed symptom onset compared to Latin-American and African-American patients<sup>5</sup>. It is possible that because clinical manifestations are more severe in African-American patients, the cognitive findings may be part of what is overall a more aggressive disease course. Race also affects MS' impact on cognition: Adult African-American patients with MS develop cognitive deficits earlier in the disease course compared to adult Caucasian patients<sup>6</sup>. This difference is also observed in pediatric MS patients. A 2010 study from the University of Alabama at Birmingham reported that African-American children affected by pediatric-onset MS performed worse on tests of complex attention and language compared to Caucasian children with MS matched by age, disease severity, gender, and socioeconomic status<sup>7</sup>.

Cognitive impairment is a common clinical feature of multiple sclerosis (MS) at both the earlier and later stages of the disease, and has a significant impact on patients' functional status and quality of life<sup>12</sup>. As with Alzheimer's disease (AD), MS patients with high levels of cognitive reserve are less likely to experience cognitive impairment<sup>12</sup>. A study by Benedict et al, 2010 followed patients with MS over a five-year period showed that those with a high cognitive reserve at

baseline experienced no loss of cognitive function, while those who started with a low cognitive reserve suffered a significant cognitive decline<sup>8</sup>.

Schulz et al., 2006 stated that the factors associated with cognitive dysfunction in this disease have not been fully elucidated yet, but several findings suggest that cognitive dysfunction could appear in the earliest stages of the disease as the first symptoms of MS<sup>9</sup>.

The evaluation of cognitive impairment in MS patients became theme of interest for health professionals since this disease affects young persons and the cognitive deficits not only reflect on emotional, social, and working activities, but also on sexuality and routine activities, what implies on loss of quality of life, even when physical disability is minimal<sup>10</sup>. For these reasons, an accurate evaluation of cognitive impairment, applying neuropsychological methods, may be a helpful instrument to the comprehension of the disease neurophysiologic aspects, as well as it can awake the sensibility for the problems with which the patients have to face<sup>2,11</sup>.

## 2. OBJECTIVES

The objective of this systematic review is to present the results of prospective and retrospective studies on cognitive alterations in MS patients. Also to highlight the relationship between MS and cognitive impairment and its risk factors.

## 3. METHODOLOGY

### *Design:*

Systematic review study for identifying the cognitive alteration in MS patients.

### *Search Strategy:*

We conducted systematic search for published studies through electronic bibliographic databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine Database, and PsycInfo in September, 2016. Selected medical subject headings were combined with key words relating to Multiple Sclerosis (MS) and Cognitive to create a search strategy to be able to use in MEDLINE and amended for use in the other databases, using appropriate controlled vocabulary, Boolean operators, and search symbols. Delimiters were: dates searched (1980–2016); research subjects (human); and language (English). The search included the literature, using reference lists and citation searching from reviews and published trials, the Science Citation Index, and also involved consulting noted experts in the field. Endnote was used to store and manage the results of the database searches.

## 4. RESULTS

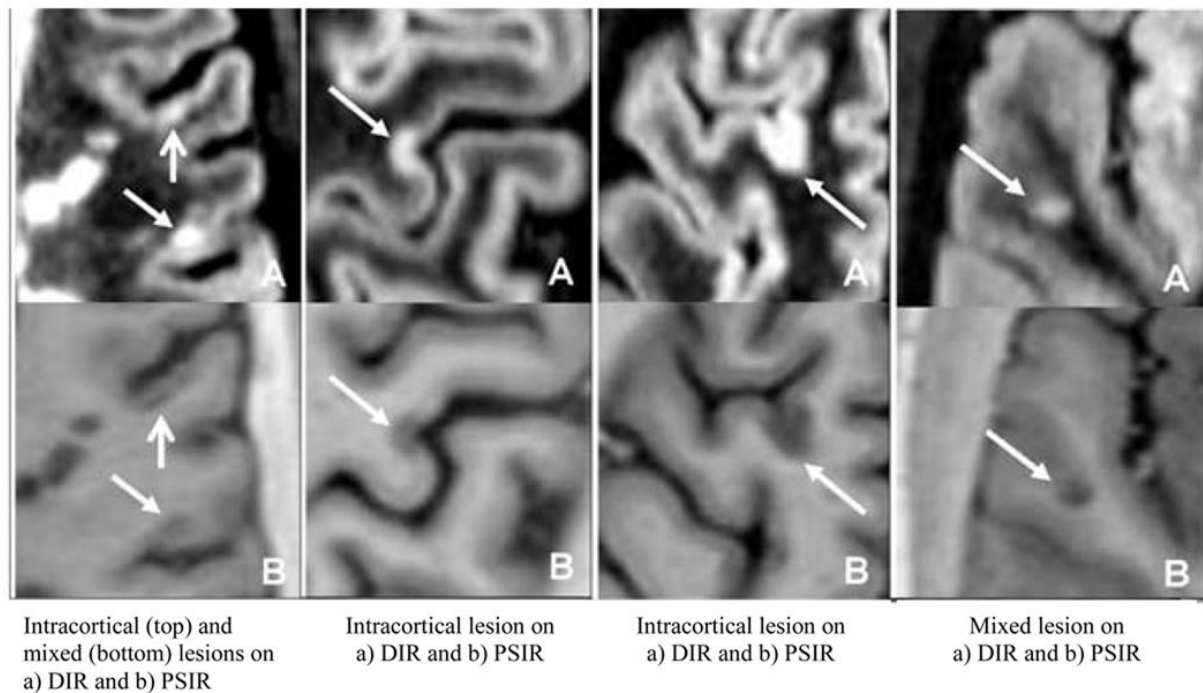
### *Anatomical alteration which participate in the mechanism of cognitive disturbance in MS patients:*

Our systematic review has identified twelve<sup>(13-24)</sup> studies discussing the mechanism underlying cognitive impairment in MS and correlation between cognitive decline in MS patients and both macro- and microscopic alteration in brain anatomy; and this has been demonstrated by using structural and functional brain imaging. Two of identified studies Morgen et al.; Dineen et al.<sup>13,14</sup> which were investigating the mechanism that could lead to cognitive disturbance among MS patients have shown recently that both gray and white-matter lesions contribute to mental dysfunction in MS. additional to that, some more old studies<sup>15,16,17</sup>. Rao et al.<sup>15</sup> correlate white-matter lesions localizations with specific cognitive impairments. Four studies Foong et al<sup>16</sup> and Sperling et al<sup>17</sup> Geurts et al.;<sup>18</sup> Sanfilippo et al.<sup>19</sup> demonstrated that there is a significant association between executive deficits and damage in the prefrontal cortex and frontal and parietal lesion burden has been shown to correlate with performance on tests of complex attention and verbal working memory. This relationship between specific white lesion location and cognitive performance was also demonstrated in early stage of MS such in study which was included in our review by Ranjeva et al<sup>20</sup> which performed investigation on patients with clinically isolated syndromes and cognition impairment and conclude that poorer performance in processing speed and working memory was associated with abnormalities in the splenium of the corpus callosum and in the right superior longitudinal fasciculus.

Nelson et al.,<sup>21</sup> study showed more cortical involvement related to MS is heterogeneous since it may arise from local demyelinating lesions, meningeal inflammation, neuronal injury, and transsynaptic degeneration **Fig.1**. As well, Piras et al.<sup>22</sup> showed selective decrease of the cortical volume was found in patients with relapsing–remitting (RR) MS and mild

cognitive deficits; this was associated with poorer performance on tests of verbal and spatial memory, attention and concentration, and verbal fluency.

Calabrese et al.<sup>23</sup> found that MS patients with cognitive deficits have more cortical lesions and more severe cortical atrophy than patients who were cognitively preserved which can contribute into the mechanism of alteration in MS. However Calabrese and Penner,<sup>24</sup> showed better approaches to understand cortical involvement which by subcortical involvement with the multiple disconnection syndrome, and have confirmed that MS-related cognitive dysfunction results from a series of domain-specific disconnection phenomena. As such, disruption of critical white-matter tracts will lead to reduced functional connectivity between cortico-cortical and cortico-subcortical cognitive processing regions, resulting in impairment to specific cognitive domains.



**Fig.1: Examples of Cortical lesions by Nelson et al.<sup>21</sup>**

### ***Most Affected Cognitive Processes***

Progressive impairment in more than one domain of intellectual function without alteration in arousal (dementia) may result from cortical or subcortical dysfunction. Cortical dementias are classically associated with dysphasia, dyscalculia, dyspraxia, agnosia, and severe amnesia in the absence of significant primary sensorimotor dysfunction<sup>31</sup>. Subcortical dementia is characterised by early psychomotor retardation and mood disturbance, with relative preservation of language, calculation, and object recognition, and by memory deficit which is greatest in free recall tasks, improving with cueing and recognition paradigms<sup>32</sup>. Although regarded as a typical subcortical dementia,<sup>33,34</sup> a subgroup of patients with multiple sclerosis shows marked impairment of abstract-conceptual reasoning, dependent on intact frontal functions<sup>34</sup> and impaired language, suggesting cortical dysfunction. In addition, memory impairment is a common complaint in patients with multiple sclerosis and was a prominent feature in our cases<sup>33</sup>.

Some studies conclude that patients with MS have trouble initially committing information to memory; the majority found that most patients have some difficulty remembering information learned in the past. In a study which was identified in this review Brissart et al.<sup>25</sup> involved 426 patients with MS, out of them 66 percent of patients had deficits in at least one recall task, while only 14 percent had difficulties making new memories<sup>25</sup>. The encoding difficulties could be due to decreased processing speed or the inability to make sense of incoming information, both of which are very difficult to measure without an extensive battery of neurocognitive tests<sup>25</sup>.

### ***Roles of Depression and Physical Disability as risk factors for Cognitive Alteration in MS patients:***

Depression is well recognized as a complication of multiple sclerosis, with an estimated lifetime prevalence of almost 50%.<sup>21</sup> There is evidence in two studies Whitlock et al.<sup>26</sup>, and McDonald et al.<sup>27</sup> that depression represents a feature of

multiple sclerosis rather than simply a reaction to the disease or comorbidity in a study controlled for physical disability. Other three<sup>28,29,30</sup> studies suggest that multiple sclerosis with the present and previous series can be heralded by a long period of depression (13 of 17 cases in previous case reports, and five of the six in the present series). As in many other neurological disorders, depression in multiple sclerosis is commonly thought to reflect white matter pathology. Depression can, however, be associated with pathology affecting the orbital and medial prefrontal cortices.<sup>24</sup> Several studies into the biology of depression have shown that depressive symptoms, both in primary affective disorders and in association with organic neurological disease, are associated with reduced temporal and frontal cortical function<sup>28,29,30</sup>.

## 5. CONCLUSION

The evaluation of cognitive impairment in MS patients became theme of interest for health professionals it seems plausible to admit that memory and processing speed impairment in MS patients is related to brain metabolism and perfusion alterations. Among the studies that integrated the present review, many aspects of memory and processing speed had been evaluated, including visual, spatial, visuospatial, work, mediate/immediate, semantic, retroactive/proactive, and recognition memory, with prejudice in all of them. The results suggest also that, although there is retention of initial informations, the neurological alterations determine reduction of late memory due to loss of fixation of these informations. These functions include the ability for planning, anticipate results and directing resources adequated to objectives. Deficits in executive functions in MS patients occur less frequently than memory or processing speed disability

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