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Cognition in multiple sclerosis: a review of neuropsychological and fMRI research

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1. ABSTRACT

Multiple Sclerosis (MS) is a disease of the central nervous system affecting millions of people worldwide. In addition to the disabling physical symptoms of MS, roughly 65% of individuals with MS also experience significant cognitive dysfunction, especially in the domains of learning/memory, processing speed (PS) and working memory (WM). The purpose of this review is to examine major topics in research on cognitive dysfunction, as well as review recent functional magnetic resonance imaging (fMRI) studies focusing on cognitive dysfunction in MS. Additionally, directions for future research are discussed.

2. INTRODUCTION

Multiple Sclerosis (MS) is a disease of the Central Nervous System (CNS) characterized by chronic inflammatory demyelination and axonal injury (1; 2). An estimated 2.5 million people worldwide are affected by MS, including 300,000 to 400,000 individuals in the United States (3-5). Indeed, MS is the most common cause of nontraumatic neurologic compromise among young adults in the United States. Symptoms of MS include fatigue, optic neuritis, diplopia, sensory disturbances, trunk or limb paresthesias (Lhermitte's sign), gait ataxia, limb weakness, and neurogenic bladder and bowel symptoms. In addition to

motor and sensory symptoms, cognitive impairment is quite common and is found in roughly 65% of people suffering from the disease (6). This article provides a review of commonly impaired cognitive domains, as well as a review of recent functional magnetic resonance imaging (fMRI) studies focusing on cognition. In addition to discussing the state of the cognitive and functional neuroimaging literatures in MS, this review provides insight and direction for future research.

3. COGNITIVE DYSFUNCTION IN MS

MS-related cognitive dysfunction was first noted by Charcot, a nineteenth century neurologist who observed cognitive slowing and memory problems among individuals with MS (7). Despite this, research into MS-related cognitive functioning had been scant until the latter half of the twentieth century, likely due to underestimates by professionals of perceived cognitive dysfunction. In fact, as late as the 1970's, Kurtzke and colleagues (8) had reported that only 3% of individuals with MS experience cognitive deficits. Since that time, however, prevalence estimates of cognitive impairment have reached as high as 50 to 70% (9). Cognitive impairment may appear as early as the first demyelinating attack (10), and may progress as disease burden increases (11).

Previous underestimates of MS-related cognitive dysfunction were likely related to the fact that intellectual functioning remains largely intact (9; 12), thereby making cognitive deficits less apparent to clinicians and researchers of the time. Crystallized knowledge in particular is resistant to MS-related cognitive changes (13). Similarly, expressive language and language comprehension remain largely intact (9), although robust deficits in verbal fluency have been identified (14). Although verbal fluency is a language task, it is also a speeded task reliant on rapid semantic retrieval. As is evident from the following discussion of cognitive dysfunction, deficits in information PS are prevalent among individuals with MS. Other cognitive domains often affected include: WM, executive functioning, visual perception, and learning and memory. The purpose of this section is to provide a snapshot of MS-related functioning in each of these domains, highlighting the current knowledge state rather than providing an exhaustive review of the literature.

3.1. Processing speed

Processing Speed (PS) has been conceptualized as the amount of time needed to process a set amount of information, or the amount of information that can be processed within a certain unit of time (15). Consistent with Charcot's original observation of MS-related cognitive slowness (7), slowed PS has been identified as one of the most robust cognitive deficits among individuals with MS (16-24). Consistent with decreased neural conduction speed secondary to demyelination (25), PS deficits are observed on even the most basic speeded tasks, including automatic processing of visual stimuli (26; 27). A meta-analysis of PS in MS portrayed a global speed deficit, with reaction time for individuals with MS increasing as a function of reaction time for healthy controls (22; 24). Reaction time discrepancies widen during choice reaction time tasks requiring differential responding (28). Although individuals with MS are slower than healthy controls during simple selective attention tasks, their accuracy remains relatively intact (29; 30), indicating that slow PS does not necessarily compromise performance accuracy when task demands are low.

This slow yet accurate performance on cognitively simple tasks degrades to slow and inaccurate as the cognitive processing demands of time-limited tasks become more complex (31; 32). For instance, Parmenter and colleagues found that performance accuracy degraded together with reaction time as a WM task (N-Back) became more challenging (29;30). The most commonly used task to measure information processing efficiency among individuals with MS is the Paced Auditory Serial Addition Task (PASAT;(9; 33)). The PASAT requires individuals to rapidly add each new aurally presented single digit to the previously presented single digit and to produce the total aloud. Performance on the PASAT, which relies on both PS and WM, is a sensitive indicator of cognitive dysfunction in MS (34).

Investigating the contributions of PS and WM to complex information processing ability in individuals with MS, Lengenfelder and colleagues found that, when allowed to work at their own pace, 70% of individuals with MS were able to produce accuracy comparable to healthy controls (31). This suggests that slowed PS is the primary cause of MS-related difficulty on complex information processing tasks. On the other hand, there remained a minority of 30% within the MS group who could not perform comparably to healthy controls despite additional time. As such, this 30% were described as exhibiting a WM deficit. Consistent with these findings, DeLuca and colleagues identified PS as the primary MS-related information processing deficit across individuals with relapsing-remitting and secondary-progressive MS; however, those in the latter group also demonstrated a concomitant WM deficit (32).

3.2. Working memory

When examining the nature of the WM deficit in MS, many researchers have relied on Baddeley's well-established multi-component model (35). In its simplest form, Baddeley's model consists of two limited capacity slave systems responsible for temporary maintenance of auditory and visuospatial information (i.e., phonological loop and visuospatial sketchpad) and a central executive responsible for allocating attentional resources to each of these slave systems, as well as actively manipulating information within each system. While some have found diminished phonological loop capacity among individuals with MS (23; 36), more recent evidence indicates a deficit within the central executive (37;38). The latter is consistent with Thornton and Raz's meta-analytic study of memory functioning in MS, which found that online maintenance of information (i.e., phonological loop) was only mildly deficient (d = .35), while the deficit in online manipulation of information (i.e., central executive) was large (d = .72) (39).

Consistent with a deficit within the central executive of WM, individuals with MS have difficulty on speeded divided attention tasks (e.g., 40). On the other hand, research on MS-related vulnerability to cognitive interference has been mixed when PS has been taken into account, with some finding a increased vulnerability to interference (41), while others have not (20; 42). As mentioned above, it remains unclear whether impairments in WM are secondary to impaired PS or an orthogonal and separate deficit.

3.3. Executive functioning

The executive functioning domain encompasses higher-order cognitive skills employed in pursuit of goals. Examples of executive functions include planning, organization, reasoning, and abstract conceptualization. Executive functioning in MS has been assessed primarily with card sorting and tower tasks, which evaluate the accuracy and efficiency of problem solving ability in the absence of explicit speed demands. In general, MS-related problem solving performance is accurate but inefficient. For instance, individuals with MS demonstrate a slower initial learning curve than controls on the Wisconsin Card Sorting Test (WCST); however, subsequent conceptualization ability is intact after this initial inefficiency (42). Also, despite intact conceptualization ability, Parmenter and collegues found that individuals with MS show cognitive inflexibility manifested by difficulty shifting cognitive sets on the WCST (30). On the Tower of London task, individuals with MS were slower to plan and execute moves; however, they did not differ from controls in their number of correct responses (20). In addition to overall slower performance relative to controls, Voelbel et al. (43) found that individuals with MS required more moves than controls to complete the Tower of London.

Arnett and colleagues investigated differences on the Tower of Hanoi task across stages of MS disease progression compared with healthy controls (44). Individuals with Relapsing-Remitting MS (RRMS) and healthy controls did not differ in overall performance or in time per move; however, individuals with chronic progressive MS (CPMS) performed worse than the RRMS and control groups on both measures. As such, analogous to DeLuca and colleagues' finding that WM deficits are more likely to emerge later in the disease (32), Arnett et al. showed that progressive disease stages are more prone to executive dysfunction than RRMS.

3.4 Interaction between processing speed and higher-order cognition

An unstated assumption throughout much of the MS literature is that PS and WM (and perhaps even executive functioning) represent separate and independent constructs. Although the contribution of PS has been neglected in current theories of WM (for review, see 45), the relationship between PS and higher order cognition has been addressed within the literature on normal aging. Salthouse hypothesized two mechanisms by which speed has a limiting effect on cognition (46). The *Limited Time Mechanism* proposes that, given an individual's slow rate of information processing, there may not be enough time for later processes to occur because the individual has already spent too much time on earlier processes. The *Simultaneity Mechanism* proposes that, because of the slow rate of executing operations, the products of earlier processing may be impoverished or degraded by the time other simultaneous processing is complete. These mechanisms suggest that slowed PS itself results in inefficient processing of information, which may then result in abnormal higher level cognitive functioning. Salthouse's mechanisms have recently been discussed in the context of MS (15).

Although there is a relationship between PS and higher order cognition in MS (18; 32; 36; 39; 47; 48), the nature of this relationship is not well understood. DeLuca and colleagues proposed two models for the interaction between PS and WM to explain their finding that individuals with RRMS exhibit PS deficits and that those with Secondary Progressive MS show both PS and WM deficits (32). The *Relative Consequence Model* proposes that individuals with MS may have a primary deficit in PS which secondarily causes deficits in other cognitive domains. As such, it is reasonable to hypothesize that higher-order deficits are secondary to a primary deficit in PS. Alternatively, the *Independent Consequence Model* allows for the possibility that later deficits (i.e., WM) emerge independently from a PS impairment, perhaps due to other disease related factors such as increased lesion burden. The interaction between PS and WM is a complicated issue that is not well understood. Future research should investigate the role of PS in models of WM, especially within clinical populations such as MS.

3.5 Visual perception

Research on MS-related visual perception deficits is limited, perhaps due to the technical challenges of measuring visual processing in the absence of motor responding. Another possible explanation for the limited research may be an assumption that MS-related visual perceptual deficits are due to primary visual impairments secondary to optic neuritis, a prevalent neurologic symptom of MS (49). Although primary visual deficits have obvious functional implications, even individuals with MS and intact visual acuity demonstrate visual processing deficits, including slowed automatic visual processing (26;27) and visual perception difficulty (50; 51). About 26% of individuals with MS demonstrate some form of visual perceptual impairment (51) including deficits in visual perceptual discrimination (6) and visual object recognition (50). Of note, given that visual perceptual deficits are demonstrated independently from other cognitive deficits (50; 51), they are likely caused by a focal deficit within visual perceptual system rather than any global degree of MS-related impairment. Even still, analogous to higher-order cognitive domains discussed above, efficiency of lower-level processes contributes to higher-order visual perception (51).

3.6 Episodic memory functioning

Memory dysfunction is one of the most common cognitive complaints among individuals with MS (9; 52). Although implicit memory is generally intact (e.g., 53),

numerous studies have documented impaired explicit memory during laboratory tasks (for review, 39). Research has also identified a linear relationship between memory dysfunction and functional disability (e.g., 54). It is important to develop an accurate neuropsychological understanding of the nature of MS-related memory dysfunction in order to design the most efficacious rehabilitation techniques.

Recent research on the nature of memory dysfunction in MS shows that most persons with MS have difficulty with the acquisition of new knowledge as opposed to retrieval from long term storage. Initially, based largely on the work of Rao and colleagues, it was thought that memory difficulty in persons with MS was due to impaired retrieval (55-58). This was based on the observation that individuals with MS demonstrated impaired free recall despite intact recognition. Free recall tasks are generally considered more effortful because individuals must provide their own retrieval cues without external assistance. As such, free recall tasks measure the *accessibility* of information in long-term storage. Because recognition tasks relieve the cognitive burden of retrieval, these tasks have been conceptualized as measuring the *availability* of information in long-term memory. As such, Rao and colleagues used recognition memory to quantify memory acquisition. Given their observation that individuals with MS demonstrated impaired free recall (accessibility) in the context of intact recognition (availability), they concluded that memory impairments in MS are due to a primary deficit in retrieval (e.g., 55).

More recent research has questioned the retrieval-based explanation of MS memory impairment. Thornton and Raz (1997) performed a meta-analysis of 36 studies comparing memory performance among individuals with MS and healthy controls (39). As expected, there was a large effect showing diminished free recall by individuals with MS. Contrary to the results of the aforementioned memory studies, however, there was also a medium effect showing reduced recognition performance by individuals with MS. The combination of deficient free recall and impaired recognition does not support a purely retrieval-based explanation of memory impairment. Rather, this points to inadequate learning (or acquisition) as the primary problem. As noted by Thornton and Raz, prior individual memory studies likely lacked the statistical power to detect a medium-sized deficit in recognition. Thornton and Raz hypothesized that memory dysfunction is probably due to a combination of both inadequate initial acquisition as well as retrieval difficulty.

DeLuca and colleagues (47; 59) directly investigated the possibility of an acquisition-based explanation of MS-related memory dysfunction. Hypothesizing that inadequate acquisition of information resulted in later recall deficits, DeLuca was the first to ensure that all participants adequately acquired the stimuli by training both MS and healthy control subjects to the same learning criterion. DeLuca and colleagues used a selective reminding paradigm, during which individuals with MS and healthy controls were asked to listen to a list of 10 words and then immediately recall it. This procedure was repeated until participants were able to correctly recall all 10 words during two consecutive trials, thereby ensuring that all participants had acquired the list. The results showed that individuals with MS required more trials in order to learn the list, thus demonstrating impaired learning in MS. However, after ensuring comparable learning, no significant differences between the groups were observed on either free recall or recognition, even up to one week following learning. Consistent with research showing normal rates of forgetting among individuals with MS (54;55;60), DeLuca found no group difference in rates of forgetting. They concluded, therefore, that MS-related memory impairment is due to deficiencies in the initial acquisition of information rather than a primary retrieval deficit. Given research showing inefficient verbal learning strategies among individuals with MS (61), providing them with additional study trials likely improved the quality of their encoding / acquisition.

In further support of the acquisition-based explanation of MS-related memory impairment, Thornton, Raz, and Tucke (62) demonstrated that qualitative differences in initial encoding have implications for later retrieval. Thornton et al. proposed that individuals with MS had difficulty encoding weakly associated word pairs in a way that would support later recall. However, if the weak cue was replaced by a strong cue during delayed cued recall, individuals with MS were able to adequately retrieval the word. In other words, even though the weakly associated words were *available* in long-term memory, the impoverished nature of their acquisition resulted in diminished *accessibility* when relying on the original weak cue. As such, consistent with the acquisition-based explanation of MS-related memory impairment, the quality of initial acquisition contributes to later retrieval. Other research has also supported the acquisition-based explanation (48; 63).

There is ample evidence that inadequate initial acquisition of information is largely responsible for episodic memory deficits. The next issue, then, is to uncover the factors which lead to impoverished / inadequate acquisition. Recent research has documented an association between information processing variables and MS-related memory impairment. For instance, in Thornton et al.'s (2002) paired associate study, individuals with MS had significantly lower WM capacity than controls (62). Also, performance on the paired associated task of individuals with MS was significantly predicted by their WM capacity. Given the absence of such a prediction for the healthy control group, it is likely that WM capacity had a limiting influence on the performance of individuals with MS. This is consistent with other research identifying a significant association between verbal memory and information processing efficiency (18; 36; 47; 48).

In sum, MS research has moved from a purely retrieval-based explanation of memory impairment to an explanation based on impoverished / inadequate acquisition, likely secondary to information processing inefficiency. This distinction has significant implications

for the cognitive rehabilitation of learning and memory problems in persons with MS. For instance, rehabilitative efforts should be focused on ways to support the adequacy and richness of acquisition, thereby making the to-be-learned material available for later retrieval.

3.7 Lifestyle, fatigue, psychological functioning

Cognitive impairment can negatively affect an individual's ability to function in everyday life and in society. Individuals with MS with cognitive impairment are less likely to be employed and may experience difficulty performing everyday life activities compared to individuals without cognitive impairment (e.g. 64-66). For example, activities such as driving a car or shopping can be more difficult in those individuals who experience cognitive difficulties (67-70). It has also been reported that interpersonal relationships and participation in social activities may be difficult in cognitively impaired individuals (66).

Fatigue is the most common self-reported symptom is MS, affecting approximately 90% of those diagnosed (71). A relationship between cognitive functioning and fatigue has been elusive, with evidence that increased self-reported fatigue over a period of time (e.g., the course of the work day) is not accompanied by degraded neuropsychological performance (72-74). However, there is some preliminary evidence that fatigue associated with sustained cognitive performance may affect cognition (71). Although the study of fatigue presents several methodological issues (i.e., operationalization), the high prevalence of fatigue merits continued empirical attention. The interested reader is referred to DeLuca (2005) for a more thorough discussion of fatigue in MS (71).

Given the dramatic physical, cognitive, and social changes associated with MS, it is not surprising that individuals with MS are at increased risk of depression. Although an association between depression and cognitive functioning had been elusive in individuals studies (e.g., 47), a meta-analysis identified a correlation between depression and WM functioning (39). Arnett and colleagues (75) found that depressed individuals with MS performed worse than non-depressed individuals with MS on tasks requiring a high degree of cognitive effort. This is consistent with the established association between low motivation and decreased initiation among depressed individuals.

4. INVESTIGATION OF COGNITIVE IMPAIRMENT IN MS USING NEUROIMAGING

Up until the last decade, researchers used neuroimaging in the study of cognitive impairment in MS only to investigate the relationship between pathology and performance on neuropsychological tasks. Studies investigating the relationship between cognition and pathology focused on the effects of lesion load and atrophy, which are quantified using standard MRI measures (i.e., T2 hyperintensities). Recently, advances in neuroimaging have prompted researchers to investigate the effects of other neuroradiologic variables, such as neurometabolism and normal-appearing white matter (NAWM) abnormalities.

Generally speaking, moderate to strong correlations have been reported to exist between neuropsychological task performance and lesion burden (e.g. 76-80). Atrophy measurements have also been shown to correlate with cognitive impairment (e.g. 81-85). In fact, compared with the variance in cognitive functioning accounted for by white matter lesion load, MS-related brain atrophy (e.g., third ventricle width) accounts for about 25% to 55% of the variance in cognitive functioning (83; 86-88).

It appears, therefore, that white matter lesion load and atrophy are correlated with cognitive performance, but much of the variance is still unaccounted for. This may be due to several factors. For one, typical MRI measures may quantify pathology, but are nonspecific in nature. For example, within lesions, multiple pathological processes may be active, such as demyelination, axonal loss, and inflammation (89; 90). It is not known how or to what degree pathological processes differentially affect cognition. Also, MS-related damage is widespread, and although damage can be locally quantified using one method, such as lesion load quantification, microscopic damage in other regions such as NAWM and Normal Appearing Grey Matter (NAGM) may not be visible using MRI. Whereas lesion load measurements are non-specific and might not reflect axonal loss, axonal damage can be examined in NAWM and NAGM using several methodologies. Further, damage to both NAWM and NAGM have both been shown to correlate with cognitive dysfunction in domains such as memory, PS, and executive dysfunction using a number of new neuroimaging methods, such as Magnetic Transfer Imaging (91), Diffusion Weighted Imaging, (92; 93) and Magnetic Resonance Spectroscopy (94-96).

4.1 Functional MRI and cognition in MS

Although structural neuroimaging techniques provide information regarding how pathology affects cognitive functioning, functional MRI (fMRI) has provided invaluable information regarding how neural networks underlying cognitive processes are affected by MS. Initially, fMRI was used to investigate motor functioning in individuals with MS (e.g. 97-100) and in the past decade, there has been an explosion of research using fMRI to examine cognitive processes in MS, as well (e.g. 101-105). Most of the focus of the cognitive research has been on WM. Recently, however, the cognitive constructs of PS, attention and memory have also been examined. The following review will cover the major findings of the fMRI studies focused on those cognitive domains.

4.1.1 Working memory

As mentioned, the most extensively studied cognitive domain in MS using fMRI is WM. WM has been widely investigated in HCs, which provides researchers with a valuable model to begin comparing differences in individuals with MS. One commonly reported observation in studies of WM is that individuals with MS have more activation than HCs in those regions typically thought to be

involved in WM processes, such as the prefrontal cortex (PFC). The PFC has been widely studied in investigations of WM, purportedly subserving both the "central executive functions" of WM, such as manipulating and updating information as well as the "slave system functions" (i.e. the maintenance of information) (106-109).

Given its sensitivity to cognitive impairment in MS, the PASAT is one of the most commonly used tasks to assess WM (and PS) in MS using fMRI. Several common findings have been observed across studies which have utilized this task (for review, see 110). First, it has been noted that in individuals with MS, activation is more dispersed throughout the brain compared to HCs during performance of the PASAT, including regions of the prefrontal cortex, parietal lobe, and anterior cingulate (e.g. 101; 102; 104). Activation differences in the PFC have been of particular interest, as it is often been reported that the MS group has increased recruitment of the PFC during PASAT performance, commonly in the right hemisphere (e.g., 101; 102). Investigators have suggested that the recruitment of this region (as well as others) are due to cerebral reorganization or task difficulty (e.g. 101; 102; 111). The potential explanations for this recruitment will be discussed at the end of this review.

Another task commonly used to assess WM using fMRI is the n-back task. During the n-back, the participant views a series of stimuli and is asked to respond when they are presented with a stimulus which matches the stimulus presented 'n' trials previously (i.e. n = 1,2,3). The advantage of using the n-back is that WM load can be manipulated to examine the effects of task difficulty.

The n-back is a popular task for assessing WM functioning both in healthy adults and individuals with MS. Typically, in HCs, n-back performance results in the activation of brain regions presumably thought to underlie WM including supplementary motor area (SMA), dorsolateral and ventrolateral PFC, posterior parietal cortex, and the anterior cingulate, among others (for review, see 112). Many studies using the n-back have focused on whether individuals with MS tend to show more or less activity within the WM circuitry compared to HCs and whether the MS group recruits additional brain regions outside of the WM circuitry. Several common findings have been observed. Generally speaking, both HCs and individuals with MS tend to activate the same brain regions within the WM network (113; 114). In two separate studies (Sweet et al., 2004 and Forn et al., 2007), it was reported that during the 2-back, although both groups (MS and HCs) activated similar brain regions within the WM network, the MS group had significantly *greater activation* in several of those regions (including DLPFC, SMA, ACC) (113; 114). However, they did not show increased activation in regions beyond WM circuitry, such as occipital regions and superior parietal regions. Therefore it appears, based on these two studies, that increased activation in the MS group is generally constricted to those regions within WM circuitry, although at least one study has reported otherwise. In that study, Wishart and colleagues found that during both the 1 and 2 back, individuals with MS had decreased activation in brain regions within WM circuitry compared to HCs, and increased activation in regions beyond the WM circuitry (115). Methodological differences, as well as sample differences likely explain the inconsistent findings. For example, Wishart and colleagues (115), included a sample of subjects with "mild RRMS," which may indicate that they were not as disabled as subjects in the other two studies (in the study by Sweet and colleagues (114), subjects had all been diagnosed for at least 10 years.) It appears that disease duration and level of disability may also play a role in the activation patterns observed in each study.

The above mentioned studies utilized the 1 and 2-back conditions to examine WM processes. However, only one study to our knowledge increased task load to include the 3-back condition as well in individuals with MS. Sweet and colleagues found that during all levels of WM demand, individuals with MS had greater activity than HCs in regions typically involved in WM such as somatosensory regions and PFC (116). However, during higher WM demands, recruitment of brain regions decreased in the MS group. Recruitment of brain regions outside of the WM circuitry was not observed. Therefore it appears that again, during a difficult WM task, individuals with MS tend to have greater activation of brain regions typically thought to subserve WM. However, it may be that as task demands increase to a certain threshold, individuals with MS are no longer able to recruit necessary cerebral resources. Future studies using the 3-back may help to elucidate the neural consequences of increased task demand.

Finally, another task which has been used to quantify WM processing in MS is the Sternberg task. The Sternberg requires subjects to view either 2 or 5 digit strings of numbers. After a brief interval of time during which they are asked to silently rehearse the number string, they are shown a target number and asked if it was present in the previously viewed string of numbers. The advantage to using the Sternberg is that WM load can be altered in two ways: either by lengthening the string of numbers or increasing the rehearsal time interval. Additionally, it requires minimal modification to be used in fMRI. Hillary and colleagues (103) found that when examining brain activation during the rehearsal time, individuals with MS had greater activity in the right hemisphere compared to the HCs, and upon closer analysis, it was shown that individuals with MS had greater right PFC and temporal lobe activation than HCs. Additionally, a negative correlation existed between right PFC activation and accuracy scores in individuals with MS, indicating that as activity in this region increased, there was a behavioral performance decrement. Interestingly, this study indicates that even when using a completely different WM paradigm, increased right PFC activation is observed in the MS group, consistent with other WM studies using the mPASAT (101; 102).

4.1.2 Executive functioning

Only one study to date has focused on executive function in MS using fMRI. Lazeron and colleagues utilized a modified version of the Tower of London, a well

known planning task with two levels of difficulty (easy vs. hard), to investigate executive functioning in MS (117). Behaviorally, the MS group performed significantly worse than the HCs on the easy level and neither group performed well on the hard stage. No significant differences in brain activation were observed when comparing HCs to the MS group on either level of difficulty. The authors speculated that advanced disease progression and high lesion load may have exhausted the ability of their MS sample to recruit additional brain regions. However, the range of disease progression in their sample was mild to moderate as determined by the Expanded Disability Status Scale (EDSS) and subjects had a disease duration of 2 to 15 years. The role of disease progression is therefore unclear. However, it is clear from these results that it is important to equate groups on task difficulty when testing for brain activation differences on cognitive tasks. Clearly more work is needed, including more detailed investigations of other areas of executive dysfunction via fMRI before any conclusions can reliably be made about the neural networks involved in executive dysfunction.

4.1.3 Processing speed

The functional neural components of PS in MS are still largely unidentified, with only one existing study performed to date (118) which used a modified version of the Symbol Digit Modalities Task (mSDMT). The results indicated that HCs had more dispersed activation than the MS group throughout the brain and more intense activity in several regions including parietal and temporal lobe. The MS group showed more intense activation than HCs in only one region: the right PFC. Additionally, it was found that behavioral performance (in terms of reaction time) was inversely correlated with activation in the right PFC (as performance slowed, activation increased). Interestingly, although the mSDMT was a PS task with minimal WM requirements, the results (increased right PFC in the MS group associated with poorer performance) are similar to that observed in previous studies of WM (101-103) and may provide evidence that regardless of task, the right PFC may be recruited by the MS group as behavioral performance decreases and the task difficulty increases.

4.1.4 Learning and memory

Despite the large body of research devoted to memory impairments in MS, there has been little fMRI research in the area of episodic memory. To our knowledge, only one study exists examining episodic memory impairment in MS using fMRI (119). In this study, researchers examined the correlation between patterns of brain activation and lesion load of individuals with MS during the encoding and retrieval of words. The authors found that during the encoding phase of the study lesion load was positively correlated with activation in the right MFG and left lingual gyrus, but during the retrieval phase of the experiment many more regions were correlated with lesion load (including: left inferior frontal, bilateral middle frontal, bilateral cingulate, left inferior parietal, bilateral thalamus, and cerebellar regions). These observations led the authors to conclude that neural recruitment may be more necessary during the retrieval phase of the paradigm, compared to the encoding phase. Based on behavioral research, these findings may be explained by a deficit in initial encoding, which would make retrieval more difficult (and therefore require additional resources). This is supported by the finding that recruitment of the right PFC was observed during the *encoding phase*. As we have noted in this review, in fMRI studies of cognition, the right PFC may be recruited as a result of cerebral challenge. One possibility therefore, is that during encoding into long term memory (when individuals with MS typically show deficits (47)) the right PFC was recruited to bolster cerebral resources. Later, during retrieval, the subjects may have had difficulty retrieving what was not well encoded and therefore needed to recruit additional brain resources during the retrieval stage. This study revealed the first step towards examining the neural underpinnings of episodic memory impairments.

4.1.5 Attention

Some aspects of attention have also been studied using fMRI in MS. Penner and colleagues sub-divided MS subjects into two groups based on their performance on cognitive tasks: mildly impaired and severely impaired (120). In two different attention tasks used in this study, it was reported that the mildly impaired group had increased activation compared to HCs in several regions including the dorsolateral PFC, parietal and temporal lobe. Interestingly, the severely impaired group did not differ from HCs in terms of brain activation, although they performed significantly worse, which the authors argued was due to a lack of functional integration of the activated brain regions. In other words, because the same regions were active as those used by HCs despite poorer performance in the severely impaired group, a lack of interaction between those regions might have resulted in poor task performance. In a separate study of attention by Nebel and colleagues, very different findings were reported (121). In this study of focused and divided attention, those MS subjects with cognitive impairment had decreased activation in regions of the PFC compared to HCs and the authors suggested that decreased activation in the PFC may have contributed to the poor performance of these subjects. Those without cognitive impairment did not have differing activation patterns from HCs during either task. The two studies (120; 121) used totally different tasks, and focused on different types of memory which likely results in their opposite findings. Both studies, however, provide important insight into the effect of cognitive impairment on brain activation.

4.2 Potential explanations for activation pattern differences in MS

4.2.1 Brain reorganization and compensation

Methodological differences among the afore-reviewed cognitive functional neuroimaging studies make it difficult to compare findings across studies. Even so, upon inspection of studies utilizing fMRI to investigate cognitive impairment in MS, several common findings have been found. Across multiple studies (but not all) examining different cognitive domains, more widespread activation throughout the brain (assessed by fMRI) in the MS group relative to HCs is often noted. Because increased activation in the MS group is sometimes paired with

"intact" task performance levels, many investigators have suggested that compensatory brain reorganization is a plausible explanation for the increased activation (101; 104; 105; 120). In other words, in order to perform at "normal" levels despite pathological damage, the brains of individuals with MS recruit additional brain regions.

This "compensation hypothesis" has stemmed largely from evidence seen in fMRI motor studies in 1) individuals with stroke and 2) MS. A large body of work exists with stroke patients describing recruitment of the non-affected hemisphere during motor tasks. As stroke patients regain function, fMRI has revealed that cortical activation patterns include both hemispheres, indicating that the brain has reorganized to recruit additional regions in order to compensate for the damage to the one side of the brain (122-124). In MS, this finding has also been observed in motor studies involving fMRI: individuals with MS tend to recruit more brain regions and show more widespread activation during motor tasks compared to HCs (e.g. 100; 125), suggesting that the increased recruitment of brain regions paired with normal functioning might imply adaptive mechanisms of the brain to compensate for disease. In cognitive studies therefore, investigators have also used compensation to explain increased activation in the MS group paired with "normal" performance levels (accuracy rates which do not differ from controls).

In addition to compensation, the term "brain reorganization" has also been used as a potential explanation for why individuals with MS have increased activation compared to HCs (e.g. 105; 126). In other words, increased activation may be directly related to or caused by pathology, which causes the brain to reorganize pathways. Brain reorganization is thought to occur as a result of neuroplasticity and can be loosely defined as the adaptive "ability of the brain to respond to various insults." (126). Reorganization may be linked to compensation (new pathways are developed which may contribute to better cognitive or physical functioning). As evidence for this hypothesis, new studies are emerging which combine both structure and function to provide evidence that the brain is reorganizing in response to pathology. For example, studies have indicated that increased lesion load is correlated with increased activation during cognitive tasks (e.g. 104; 119).

4.2.2 Task effort

Although the brain reorganization/compensation hypothesis is an attractive one, there are several alternative hypotheses to consider. One potential alternative hypothesis is that increased activation is related to increased task effort (111). There is evidence in support of the notion that increased activation may be partly due to increased demand on cerebral resources, and may be associated with poorer performance, rather than improved performance. At least three studies to date have reported a negative relationship between activation increases and behavioral performance (102; 103; 118). The pairing of increased activation with decreases in performance does not support the notion that increased activation is compensatory or beneficial.

Further support for the "task effort" hypothesis can be found in cognitive studies involving other clinical populations, as well as HCs. For example, in WM studies of HCs, it has been reported that as task load increases, there is increased activation of the right PFC (108; 127; 128) thereby implicating that increased recruitment of this region is associated with increased cerebral effort. Furthermore, in individuals with TBI, increased brain activation in several regions has been associated with poorer performance (129; 130). Therefore, because increased activation is often associated with poorer performance, it may be partly due to increased demand of the task which in turn increases the demand on the cerebral resources.

4.2.3 Cognitive fatigue

Yet another explanation for increased activation in MS during cognitive task performance may be related to those individuals experiencing greater levels of cognitive fatigue (116; 131). A common complaint in MS is fatigue (both cognitive and physical) (71), and at least one study has attempted to examine whether cognitive fatigue may be related in some way to differences in patterns of activation in MS (131). DeLuca and colleagues examined the brain activation of individuals with MS over the course of a sustained attention/PS task (the modified SDMT). Individuals with MS showed increases in activation over time, compared to HCs, who showed decreases in activation over time in several brain regions thought to be involved in cognitive fatigue. Although they did not measure fatigue subjectively, the finding that over time, HCs and individuals with MS showed very different activation patterns led the researchers to hypothesize that increased activation in the MS group might be indicative of cognitive fatigue. This is the only study to our knowledge which has attempted to examine cognitive fatigue with objective cognitive performance during fMRI acquisition in MS. It represents an important first step at examining the potential influence of fatigue on cerebral activation.

4.2.4 Decreased activation in MS

In addition to increased recruitment of brain regions in the MS group compared to HCs, multiple studies report decreased activation in the MS group compared to HCs (114-116). One potential explanation for this under-recruitment may be related to axonal loss, resulting in an inability of the brain to properly utilize damaged brain regions (132). According to the "axonal hypothesis," (see 133 for review), in MS, axonal loss accumulates throughout the course of the disease to a point at which the brain is no longer able to compensate, which may result in a failure to activate brain regions to the same extent as HCs. There is also evidence that in MS there is reduced cerebral blood flow to both lesioned areas and damaged NAWM (134) which may also lead to decreased activation (110; 135). The danger here is that decreased activation is often interpreted as being associated with the neural process involved in performing the task (i.e. WM ability), when it may actually be a result of pathology or vascular changes unrelated to task performance. It has been recently suggested that all fMRI investigations of subjects with brain disease include ways to quantify and control for

vascular and pathological changes in order to more closely examine brain activation which is actually related to the task (135).

5. CONCLUSIONS and FUTURE DIRECTIONS FOR RESEARCH ON COGNITIVE IMPAIRMENT IN MS

Given that the average age of onset for MS falls in young to mid adulthood, those diagnosed are often at the beginning of their careers and family lives. In addition to the disabling physical symptoms, the cognitive impairments associated with MS negatively impact many aspects of an individual's life, including interpersonal relationships, ability to work, and performance of everyday tasks. Research advances using both behavioral and fMRI methods have started to shed light on the nature of MS-related cognitive dysfunction.

The last quarter century has brought about a significant increase in our knowledge of MS-related cognitive dysfunction, including the high prevalence of slowed PS and memory difficulty. Future research should continue to focus on these issues to more specifically identify the source of the cognitive deficits seen in MS. Specifically, it is still unclear whether various cognitive deficits identified in MS (e.g. new learning, executive dysfunction, WM decrements) are due to decreased PS or whether they develop independently. This issue is vital to our ability to improve cognition in MS. If PS deficits are the source of the various other cognitive deficits seen in MS, then an effective treatment for PS deficits in MS will greatly improve cognitive functioning in MS, thus positively impacting quality of life. However, if the deficits seen in MS rise independently of one another, researchers must work to develop multiple treatment options for the specific cognitive problem a given individual is experiencing. MS related cognitive dysfunction has been shown to significantly impact the everyday life of persons with MS, even more so than the MS-related physical deficits (54; 136). Thus the development of effective treatment protocols for the cognitive deficits identified in MS is of the utmost importance. Given the recent discovery of inefficient acquisition as the principal cause of MS-related memory dysfunction, researchers have begun to develop techniques to support adequate encoding of to-be-learned information (e.g., 137). However, rehabilitation research is also necessary but currently lacking, in other areas of cognitive dysfunction, including PS, WM, and executive functioning (see 138 for a review).

MS-related fatigue also has a tremendous impact on an individual's ability to function in daily life. Yet, the construct of fatigue is still poorly understood. Despite self-reported cognitive difficulties due to fatigue among individuals with MS, a relationship between fatigue and objective neuropsychological/cognitive performance has been elusive (for review, see 71; 131). Future research should focus on improving our understanding of the general construct of fatigue, in an effort to improve our ability to objectively measure fatigue across populations, while also focusing on the impact of fatigue to the overall functioning of persons with MS. As this line of research progresses, we will then be able to tackle more specific fatigue-related issues in MS, such as the relationship between fatigue and cognition, the impact of fatigue on daily life and most importantly the development of effective treatments for fatigue in MS.

Recent advance in technology have provided us with tremendous opportunities to view the functioning brain. fMRI has only been applied to MS in the past 10 years. While this research has begun to focus on the brain's response to cognitive dysfunction, it has also left us with the formation of additional questions that will take years of neuroimaging research to address. For example, most MS studies to date show increased activation in specific brain regions (102; 104; 105; 113), while still others have reported decreased activation (114-116). It is not yet clear why activation increases in some situations and decreases in others. Future studies should attempt to address these seemingly discrepant findings to help improve our understanding of what variables may affect activation patterns and the impact of activation on cognition. Other variables not yet investigated may play a role in this phenomenon, such as the type and size of nearby MS lesions, NAWM, etc. These variables are ripe for future investigations. Related to this issue, recent studies have shown a relationship between increased right PFC and decreased cognitive performance (102; 103). The reason for this inverse relationship remains unclear as it is counterintuitive to the compensation hypothesis. Future research should examine the source of this relationship in an effort to increase our understanding of the alternate patterns of activation in MS, as well as in other neurological populations. Additionally, to further test the hypothesis that the brain is reorganizing in response to pathology, future studies should continue to combine both structural techniques such as MRS, or DTI with fMRI and other functional imaging techniques (i.e functional near infrared spectroscopy) to help investigators determine if increased (or decreased) activation is correlated with pathology and every day life activity. In addition to examining the influence of different types of brain pathology and alterations in brain activation, there are multiple variables intrinsic to our functional neuroimaging test paradigms that require more investigation. For example, the role of task effort still needs to be clearly delineated. To test the "task effort" hypothesis, investigators could potentially examine activation patterns at differing levels of task demand to see if activation patterns are modulated by increased task effort. Additionally, there is new functional neuroimaging evidence to support that fatigue may be associated with altered cerebral activation patterns in MS (131). Future research should examine the role of fatigue, as well as other variables such as depression, in understanding the new functional neuroimaging findings.

Finally, both cognitive and fMRI studies in MS should continue to examine factors that maximize cognitive functioning in this population. To date, only one study has focused on the effects of drug treatment on fMRI activation patterns in MS (139) but the findings indicated that drug

treatment may "normalize" activation patterns in MS, a finding that certainly requires replication and further investigation. The effects of exercise and cardiorespiratory fitness on cognitive dysfunction has recently been investigated using fMRI, and it was reported that individuals with MS who have greater cardiorespiratory health showed better performance on PASAT and greater recruitment of the PFC (140). The examination of the effects of drugs, exercise and other treatments on cerebral activation patterns is thus a new exciting line of research which may help investigators understand the brain's response to disease and potential mechanisms for treating cognitive impairment.

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