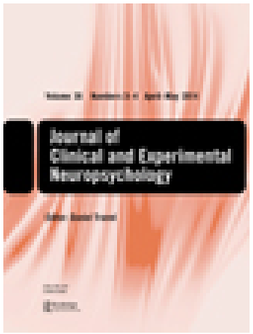

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Journal of Clinical and Experimental Neuropsychology

ISSN: 1380-3395 (Print) 1744-411X (Online) Journal homepage: http://www.tandfonline.com/loi/ncen20

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To cite this article: Cristina A. F. Roman & Peter A. Arnett (2016): Structural brain indices and executive functioning in multiple sclerosis: A review, Journal of Clinical and Experimental Neuropsychology, DOI: 10.1080/13803395.2015.1105199

To link to this article: http://dx.doi.org/10.1080/13803395.2015.1105199

Published online: 12 Jan 2016.

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 2016
http://dx.doi.org/10.1080/13803395.2015.1105199

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Structural brain indices and executive functioning in multiple sclerosis: A review

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ABSTRACT

Multiple sclerosis (MS) is a neurological disease characterized by lesion-induced white matter deterioration. Brain atrophy and damage to normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) have also been identified as consequences of MS. Neuroimaging has played an integral role in investigating the effects of white and gray matter damage across the three primary clinical phenotypes of the disease—primary progressive (PPMS), relapsing remitting (RRMS), and secondary progressive (SPMS) MS. Both conventional (e.g., T1-weighted imaged) and nonconventional (e.g., diffusion tensor imaging) neuroimaging methods have yielded important information regarding the structural integrity of the brain during the course of the disease. Moreover, it has provided the opportunity to explore the relationship between structural brain indices and cognitive functioning, such as executive functioning, in MS. In this paper, we provide a brief overview of executive functioning in MS, a general review of how structural damage presents in MS by way of sclerotic lesions, atrophy, and microstructural white matter damage, and, finally, how structural brain damage relates to executive dysfunction.

ARTICLE HISTORY
Received 4 March 2015
Accepted 2 October 2015

KEYWORDS
Multiple sclerosis; executive functioning; diffusion tensor imaging; atrophy; lesions

Multiple sclerosis (MS) affects approximately 2.3 million people worldwide, although true estimates of the prevalence of MS are difficult to identify due to the inconsistency in reporting of new cases and the possibility of an absence of symptoms for many years (National Multiple Sclerosis Society, 2015). MS is a debilitating degenerative disease of the central nervous system that affects approximately 2.3 million people worldwide (National Multiple Sclerosis Society, 2015). It is characterized by a recurrent inflammatory response (i.e., attack) within the central nervous system that results in damaging sclerotic lesions, demyelination, axonal loss, and gliosis (Paty & Ebers, 1998; Raine, McFarland, & Hohlfeld, 2008). Brain atrophy, and white and gray matter damage in normal appearing white matter (NAWM) and gray matter (NAGM) have also been identified as neuropathological consequences of MS and, along with lesions, have been linked to cognitive difficulties in various domains, including executive functioning (Calabrese et al., 2009; Genova, DeLuca, Chiaravalloti, & Wylie, 2014; Lazeron et al., 2005; Papadopoulou et al., 2013; Riccitelli et al., 2011; Yu et al., 2012). Magnetic resonance imaging (MRI) has proved to be a powerful diagnostic tool for detecting and measuring lesions, observing brain atrophy, and evaluating white and gray matter pathology. While functional MRI has proven useful in evaluating behavioral functioning and dysfunction in vivo, it is thought that structural damage underlies these functional deficits and is therefore the focus of this review. Structural images obtained through conventional MRI, such as T1- and T2-weighted images, allow for the quantification of white matter damage (i.e., lesions) and brain atrophy in MS, while more nonconventional neuroimaging, such as diffusion tensor imaging (DTI), offers a more precise look at the microstructure of white and gray matter. The following review seeks to explore the relationship between structural brain indices (i.e.,

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Authors report no competing interests.

lesions, atrophy, NAWM, NAGM) and executive functioning. First, a brief overview of structural brain damage in MS is presented, followed by a summary of executive dysfunction. The authors then present a detailed, up-to-date review of the relationship between structural brain indices and executive functioning in MS.

Regional MRI studies of sclerotic lesions have pointed to a characteristic distribution pattern in central white matter, often involving periventricular areas, corpus callosum, and central semiovale (Calabrese et al., 2010; Filli et al., 2012; Narayanan et al., 1997). The anterior cingulate and gray matter, such as frontotemporal areas and the motor cortex, have also been identified as areas that show a significant distribution and frequency of sclerotic lesions (Calabrese et al., 2010; Kidd et al., 1999; Lassmann, Bruck, & Lucchinetti, 2007). The presence of lesions has been shown to differ across the primary clinical phenotypes of MS, which include: primary progressive MS (PPMS), characterized by a continuous progression of the disease over time with no distinct relapses; relapsing remitting MS, RRMS, characterized by clearly defined disease relapses followed by full recovery and no progression of the disease in between relapses; secondary progressive MS (SPMS), which starts as RRMS but is followed by a worsening of the disease, regardless of whether relapses occur or not; and progressive relapsing MS (PRMS), which has a progressive disease course from onset with relapses occurring later in the disease, and despite patients' condition of recovery, they continue to experience progression between relapses (Lublin & Reingold, 1996). Overall, individuals with SPMS show a higher lesion probability than individuals with RRMS and a greater number of larger, confluent lesions than individuals with PPMS, especially in periventricular areas (Filli et al., 2012; Thompson et al., 1991) . Clinically isolated syndrome (CIS) is used to describe the first episode of inflammation and demyelination in the CNS, which can sometimes lead to MS; however, since CIS does not necessarily represent a full onset or diagnosis of MS, it is not the focus of this paper. Lesion differences between PPMS and RRMS groups are not as stark, however. Calabrese et al. (2010) showed a greater occurrence and widespread effect of sclerotic lesions in individuals with PPMS than in individuals with RRMS, but these differences were not significant.

Brain atrophy has also been shown to be a consequence of MS (Chard et al., 2004; De Stefano et al., 2003; Riccitelli et al., 2012).Voxel-based morphometry (VBM; Ashburner & Friston, 2000; Wright et al., 1995), introduced in 1995 by Wright and colleagues, was developed to characterize regional cerebral gray and white matter. VBM analyses require normalization of high-resolution images and gray matter segmentation and smoothing, and finally voxel-wise comparisons between groups are conducted (Ashburner & Friston, 2000). VBM allows researchers to answer the question: How do groups differ in brain structure (i.e., how do the intensities differ between groups in specific regions?)? Another program, FreeSurfer, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999), can also be used to investigate structural brain differences in MS. First, T1 images are corrected for motion, non-brain tissue is removed, images are transformed into Talairach space, and then white and gray matter are segmented, white matter/gray matter boundaries are formalized, and a topology correction is conducted (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Fischl, et al., 2004; Fischl et al., 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl, van der Kouwe, et al., 2004; Han et al., 2006; Jovicich et al., 2006; Reuter, Rosas, & Fischl, 2010; Reuter, Schmansky, Rosas, & Fischl, 2012; Segonne et al., 2004). These methods provide images that can be further processed to analyze cortical thickness, volume quantification of subcortical structures, measurement of cortical folding patters, parcellation of cortical regions, and sulcal depth. Additional of brain atrophy include normalized brain volume (NBV), normalized neocortical gray matter volume (NCV), relative brain volume (RBV), gray matter volume (GMV), white matter volume (WMV), brain intracranial volume ratio (BICVR), and third ventricle size. With these methods and measurements in mind, and in the context of this review, atrophy will represent decreases in whole brain matter, white matter, gray matter, cortical thinning, or ventricle size, as measured by any of the above. Longitudinal MRI studies of MS have shown significant decreases in gray and white matter volumes compared to those in healthy controls (Chard et al., 2004; Fisher, Lee, Nakamura, & Rudick, 2008). These changes are dependent on disease severity, with individuals who convert from RRMS to SPMS showing lower baseline gray and white matter volumes and greater atrophy over time than individuals with RRMS who never convert (Fisher et al., 2008). Atrophy in gray and white

matter can be detected very early on in MS, but the trajectory of change between these two tissue types appears to differ (Chard et al., 2004; De Stefano et al., 2003; Riccitelli et al., 2012). Chard et al. (2004) found that at baseline, persons with MS showed significant differences in white matter volume but no differences in gray matter volume compared to healthy controls; however, after an 18-month follow-up, there were significant differences in the rate of change of gray matter volume but no significant changes in white matter volume.

The aforementioned studies demonstrate the effectiveness of conventional MRI to quantify structural brain damage and abnormalities in MS; however, white and gray matter pathology outside of damaged tissue, known as NAWM and NAGM, respectively, is harder to quantify with conventional MRI and therefore requires more advanced techniques to identify damage. Diffusion tensor imaging (DTI) is a neuroimaging technique that uses the three-dimensional diffusion of water to evaluate the microstructure of white matter tracts in the brain. Various DTI measures can be used to examine the microstructural integrity of white matter in individuals with MS. The collinear structure of white matter enables DTI to provide information about the directional coherence (anisotropy) of water diffusion, thereby providing information about the microstructural integrity of white matter. Three mutually perpendicular eigenvectors with eigenvalues λ_1 (primary/major), λ_2 (minor), and λ_3 (minor) are derived from the diffusion tensor and are used within numerous DTI analysis pipelines to calculate diffusion metrics, such as: fractional anisotropy (FA; a measure of the variance between the three eigenvalues), mean diffusivity (MD; an average of the three eigenvalues), axial diffusivity (AD; a measure of the primary eigenvalue, parallel to white matter tract), and radial diffusivity (RD; the average of the two minor eigenvalues, perpendicular to white matter tract). Directional measures of diffusivity, RD and AD, provide more specific information about the microstructure of white matter. Animal studies have shown, for example, that RD reflects demyelination, whereas AD is more representative of axonal damage (Song et al., 2002; Song et al., 2005).

Recently, DTI has begun to gain momentum as an effective neuroimaging technique to examine demyelination in the white and gray matter of individuals with MS. Filippi, Cercignani, Inglese, Horsfield, and Comi (2001), for example, used DTI to examine tissue damage in NAWM and lesions in a mixed sample of 78 individuals with RRMS, SPMS, or PPMS and 20 healthy controls. The data showed that NAWM in individuals with MS is compromised compared to that in healthy controls, indicating that white matter damage in MS can occur outside of focal lesion areas that do not appear to be abnormal on conventional MRI scans. Additional DTI studies have replicated these results and have shown the ability of DTI to better characterize white matter lesions, NAWM, and NAGM than conventional MRI (Elshafey, Hassanien, & Khahil, 2014; Oreja-Guevara et al., 2005; Roosendaal et al., 2009; Rovaris et al., 2005; Senda et al., 2012; Werring, Clark, Barker, Thompson, & Miller, 1999). Major white matter tracts, such as the corpus callosum, fornices, corona radiata, inferior and superior longitudinal fasciculi, and internal capsule, have been found to have abnormal diffusivity patterns compared to those of healthy controls, which points to compromised white matter integrity (Liu et al., 2012; Ozturk et al., 2010; Roosendaal et al., 2009; Sigal, Shmuel, Mark, Gil, & Anat, 2012). DTI is not limited to examining damage in NAWM, however. There has been growing evidence that MS is not purely a demyelinating disease of white matter, but rather a demyelinating disease of white *and* gray matter (Sander & Frankfurt, 1898, and Schob, 1907, as cited in Honce, 2013). Rovaris et al. (2005) were among the first to use DTI to show that MD increased in NAGM over a 15-month period in individuals with MS independent of lesion load and brain volume. These results were supported by Oreja-Guevara et al. (2005), who also demonstrated that that changes in NAGM occurred over time, independent of whole brain and gray matter volumes.

Sclerotic lesions, brain atrophy, and NAWM and NAGM damage not only represent the neuropathological consequences of MS, but also provide a plausible biological substrate for cognitive impairment in MS patients. Cognitive impairment is widespread in MS, affecting approximately 43% to 70% of individuals at all stages of the disease (Amato, Ponziani, Siracusa, & Sorbi, 2001; Peyser, Rao, LaRocca, & Kaplan, 1990; Rao, Leo, Bernardin, & Unverzagt, 1991). Executive functioning is a cognitive domain that is often impaired in MS, influencing work, social, and everyday functioning (Basso et al., 2008; Chiaravalloti & DeLuca, 2008; Foong et al., 1997; Kalmar, Gaudino, Moore, Halper, & DeLuca, 2008; Preston, Hammersley, & Gallagher, 2013; Strober,

Rao, Lee, Fischer, & Rudick, 2014). Lezak, Howieson, Bigler, and Tranel (2012) defined executive functioning as the ability to respond and adapt to novel situations, which involves volition, planning, purposeful action, and effective performance. Executive processes require an individual to diverge from routine, reflect on future goals and possible consequences, engage in decision making or planning, and correct for errors in order to respond in an original, goal-directed way (Baron, 2004; Shallice, 1990). Working memory, which is responsible for the short-term storage and processing of information, has also been shown to be a component of executive functioning. Baddeley and Hitch (1977) were among the first to describe the three-component model of working memory—the articulatory loop and visuospatial sketchpad (both considered "slave systems") and the "central executive." The "slave system" components are thought to maintain acoustic and visual information, while the central executive component is thought to control more complex information processing and attentional faculties. Tasks of working memory, such as the Paced Auditory Serial Addition Task (PASAT), rely heavily on the articulatory loop and central executive components and can therefore be considered as an executive-working-memory task rather than a simple attention or processing-speed task.

Various neuropsychological tests, such as the Wisconsin Card Sorting Test (WCST; Beatty, Goodkin, Monson, & Beatty, 1989; Beatty & Monson, 1996; Parmenter et al., 2007), Delis–Kaplan Executive Function System (D-KEFS; Drew, Tippett, Starkey, & Isler, 2008; Parmenter et al., 2007), Tower of Hanoi test (Arnett et al., 1997), verbal fluency tests (Beatty, 2002; Henry & Beatty, 2006; Strober et al., 2014), California Card Sorting Test (CCST; Beatty, Hames, Blanco, Paul, & Wilbanks, 1995; Beatty & Monson, 1996), and the PASAT (Rao et al., 1991; Rosti, Hamalainen, Koivisto, & Hokkanen, 2006), have been used to examine the primary components of executive functioning, including planning, shifting, problem solving, inhibition, and working memory.

With the above considerations in mind, the purpose of the current review is to explore the relationship between the structural neuropathology of MS and executive functioning. A brief overview of executive functioning in MS is provided, followed by a review of how deficits in executive processes relate to lesions, atrophy, and damage in NAWM and NAGM. Lastly, implications and suggestions for future research are provided.

Executive functioning in MS

Individuals with MS show significant deficits in executive processes that have been linked to disability, mood, poor quality of life, and subjective difficulties (Arnett, 2005; Arnett et al., 1999; Arnett & Randolph, 2006; Carrieri et al., 2013; Matotek, Saling, Gates, & Sedal, 2001). In a large-scale New Zealand study, Drew et al. (2008) used all subtests of the D-KEFS to examine executive dysfunction in 95 participants with MS. Results showed the greatest impairment of scores (1 standard deviation or more below the mean) on fluency switching, color–word inhibition, trails number–letter switching, and letter fluency. These results were consistent with those of Parmenter et al. (2007), who showed that performance on the D-KEFS sorting test was significantly different between individuals with MS and healthy controls, with persons with MS having fewer sorts, a smaller description score, and more repeated sorts. In addition, individuals with RRMS performed better than individuals with SPMS on the number of identified categories and quality of description.

Additional evidence for executive dysfunction in individuals with MS can be seen in studies looking at performance on the WCST and CCST, which test shifting, planning, and problem solving. Individuals with MS perform worse on these tests than healthy controls, and it is suggested that these deficits are due, in part, to problems with identifying sorting concepts, a tendency to make errors, and more perseverative responses (Beatty et al., 1989; Beatty et al., 1995; Beatty & Monson, 1996; Heaton, Nelson, Thompson, Burks, & Franklin, 1985). Disparities in performance scores on the WCST among different clinical phenotypes of MS have also been identified. In an early study by Rao, Hammeke, and Speech (1987), individuals with RRMS and chronic progressive MS[1] (CPMS) were compared to an age-matched chronic back

[1]Chronic progressive multiple sclerosis (CPMS) is a term formerly used to encompass all progressive types of MS. Currently, CPMS is composed of two separate types of progressive MS: PPMS and SPMS. These phenotypes of MS denote a "progressive" or continuous accumulation of neurological deficits over time (Fitzner & Simons, 2010).

pain control group. Individuals with CPMS identified fewer categories than the control group and had a greater number of perseverative errors and responses, but the RRMS group performance did not significantly differ from the control group. Arnett et al. (1997) further pointed to planning deficits in individuals with MS in their examination of performance on the Tower of Hanoi test, showing that individuals with CPMS took longer to plan moves and had fewer correct solutions overall than individuals with RRMS and healthy control subjects. When the RRMS group was removed from the analyses, the group differences held, but not when the CPMS group was removed; thus, the CPMS group accounted for performance disparities between the MS group and healthy controls. While these studies may point to better executive functioning in individuals with RRMS than in those with more progressive types of MS (i.e., PPMS, SPMS), one should not discount the prevalence of executive dysfunction across all phenotypes of MS, including RRMS. Garcia, Plasencia, Benito, Gomez, and Marcos (2009), for example, showed that individuals with RRMS had decreased executive performance on tests involving conceptualizing, categorizing, maintenance of nonautomatic strategies, and temporal ordering. Additional studies have also shown executive dysfunction in individuals with RRMS (Arango-Lasprilla, DeLuca, and Chiaravalloti, 2007; Roca et al., 2008; Ruggieri et al., 2003).

Individuals with MS also show deficits in domains of executive functioning involving working memory and verbal fluency (Berrigan et al., 2013; Connick, Kolappan, Thomas, & Chandran, 2012; Parmenter, Shucard, Benedict, & Shucard, 2006). The PASAT, an information-processing and working-memory test, has proved to be crucial for the examination of cognitive dysfunction in MS. In fact, the PASAT was chosen as the sole measure to assess cognition in the Multiple Sclerosis Functional Composite (MSFC), which, along with the Timed 25-Foot Walk and 9-Hole Peg Test, is used to assess clinical outcome in individuals with MS (Fischer, Rudick, Cutter, & Reingold, 1999). Performance by persons with MS on the PASAT often reflects fewer correct answers, more missing answers, a decreased dyad score (i.e., the number of correct responses preceded by a correct response), and more errors than in healthy controls (Rosti et al., 2006). Verbal fluency has also been found to be sensitive to cognitive changes in MS. Verbal and semantic fluency measures, such as the Controlled Word Association Test (COWAT) and animal naming, have been shown to discriminate between individuals with MS and healthy controls (Beatty, 2002). Matotek et al. (2001) found that individuals with mild MS performed worse than healthy controls on tests of verbal fluency (i.e., storytelling test); individuals with MS had more false starts, repetitions, and unfinished sentences, and verbal fluency performance also correlated with working memory. Furthermore, Henry and Beatty (2006) reviewed 35 studies of phonemic and semantic fluency and found individuals with MS to be significantly more impaired than healthy controls. Performances on phonemic and semantic fluency tests were found to be more sensitive to MS than that on the Boston Naming Test, and phonemic fluency performance was more sensitive to MS than verbal intelligence (VIQ). It is important to note that recent studies (Genova et al., 2014; Leavitt, Wylie, Krch, Chiaravalloti, & DeLuca, 2014) have pointed to the role of processing speed in executive dysfunction, such that when processing speed is accounted for, performance on tests of executive functioning are no longer significantly lower in individuals with MS than in healthy controls. While these studies shed an important light on the potential role of processing speed on executive functioning in individuals with MS, numerous studies and reviews have shown that executive functioning still stands as an impaired cognitive domain in MS (Arnett & Strober, 2011; Parmenter et al., 2007; Rogers & Panegyres, 2007; Strober et al., 2014). Furthermore, one cannot discount the fact that executive functioning encompasses numerous components (i.e., planning, abstract reasoning, working memory, inhibition, etc.) that were not all accounted for by Genova et al.'s (2014) and Leavitt et al.'s (2014) studies; therefore, it is difficult to assume that processing speed serves as the driving force for all executive processes in MS, especially when examining higher level executive processes. As a result, it is important not to discount the domain of executive functioning in MS, but instead examine it and its relationship with neural correlates.

Association with lesions

White matter and cortical lesions have been associated with performance on a number of executive functioning tests. Rao, Leo, Haughton, St Aubin-Faubert, and Bernardin (1989) were among the first to examine the relationship between

impairment on executive functioning tests and sclerotic lesions. In their study, 53 individuals with MS were administered the WCST, Stroop Color–Word Interference Test, PASAT, COWAT, and Category Word Generation Test. Results indicated that total lesion area (TLA) was the best predictor of impaired performance on the Stroop Color–Word Interference Test, WCST, and Category Word Generation Test. Swirsky-Sacchetti et al. (1992) found similar results between TLA and the WCST and COWAT and, through regional analysis, showed that lesions in the left frontal region best predicted performance on the WCST and COWAT. Regional sclerotic lesions have been further linked to the WCST through examinations of frontal lobe lesions. Arnett et al. (1994), for example, examined performance on the WCST between individuals with MS with a high ratio of frontal white matter lesions (MS-F), those with a low ratio of frontal white matter lesions (MS-NF), and an MS control group (MS-C) with minimal lesions overall. They found that the MS-F group completed significantly fewer categories on the WCST, made more total errors, and had more perseverative responses than the MS-NF and MS-C groups. No significant differences in WCST performance were found between the MS-NF and MS-C groups. Other subsequent studies of frontal lobe lesions showed significant associations with the Stroop Color–Word Interference Test, verbal fluency, and spatial working memory; however, some of these results became nonsignificant after controlling for TLA (Foong et al., 1997; Rovaris et al., 1998).

As part of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), the PASAT has been widely used to assess cognitive impairment in MS, including deficits in executive functioning. Studies exploring the relationship between the PASAT and sclerotic lesions have found significant correlations between performance and total lesion volume (TLV) and frontal, parietal, and temporal lesions (Calabrese et al., 2009; Lazeron et al., 2005; Papadopoulou et al., 2013). Relationships between frontal and parietal lesions and PASAT performance have also been shown to remain stable longitudinally (Sperling et al., 2001). Moreover, serial assessments of cognitive impairment and sclerotic lesions have found that individuals with MS who show consistent increases in TLV over a 1-year period have worse performance on the PASAT than those whose TLV vacillated or remained stable over time (Hohol et al., 1997).

Findings related to verbal fluency have been more variable, with some studies showing strong relationships between verbal fluency tests (i.e., Word List Generation Test, category fluency) and number and volume of cortical lesions, volume of white matter lesions, and total and regional lesion loads (Calabrese et al., 2009; Foong et al., 1997; Lazeron et al., 2005), while others have shown minimal or no relationship between verbal fluency and lesion load (Fulton et al., 1999; Hohol et al., 1997; Rovaris et al., 1998). These conflicting results may reflect variations in the type and number of lesion measurements used. For example, those studies that found a relationship between sclerotic lesions and performance on verbal fluency tests used a number of different measures within each study to quantify lesions, such as various regional lesion measures, cortical and white matter lesion volumes, and number of cortical and white matter lesions; studies that did not find significant results most often relied on broader total lesion measurements. Therefore, it is possible that lesion loads in more specific regions or brain parenchyma need to be examined in order to assess their influence on verbal fluency.

Association with atrophy

As previously noted, various measures of atrophy of the brain (i.e., NBV, NCV, RBV, GMV, WMV, and third ventricle width) have been used to evaluate possible neural correlates of cognitive dysfunction in MS. Although some measurements have been found to be more robust than others in predicting cognitive performance, results point to a clear link between brain atrophy and cognitive impairment in MS groups. Examinations of executive functioning and atrophy reflect these findings by showing a significant association between decreased brain volume and poor performance on executive tests. Lazeron et al. (2005), for example, found strong correlations between RBV and performance on the PASAT and the Word List Generation (WLG) test in 82 individuals with MS. Calabrese et al. (2009) found similar results between the WLG test and NBV and NCV in individuals with RRMS, but did not find a significant relationship between the PASAT and brain atrophy measures.

Regional examinations of brain atrophy have examined the role of third ventricle width and frontal lobe pathology in relation to executive functioning. Results from Benedict et al. (2004)

showed that third ventricle width significantly predicted PASAT performance; however, when third ventricle width was removed from their analysis, brain parenchymal fraction became the best predictor of PASAT score, even after controlling for age and premorbid intelligence. An earlier study by Benedict et al. (2002) found a similar relationship between PASAT performance and third ventricle width, but demonstrated that when regional cortical measures were included in the model along with third ventricle width, atrophy in the right superior frontal lobe accounted for a significant amount of variance in PASAT performance. Locatelli, Zivadinov, Grop, and Zorzon (2004) further investigated the relationship between frontal lobe atrophy and executive functioning in a sample of 39 individuals with RRMS. Each patient was administered a battery of neuropsychological tests, including the PASAT and Stroop Color–Word Interference Test; regional brain parenchymal fraction (RBPF) and regional brain parenchymal volume (RBPV) were calculated and used as measurements of brain atrophy. The authors found that performance on the PASAT and that on the Stroop Color–Word Interference Test were each independently associated with RBPF of the frontal lobes, and the magnitude of these correlations was approximately three times higher than those with RBPV.

Studies exploring the independent roles of white and gray matter pathology in MS have offered additional insight into how brain atrophy influences executive functioning. Edwards, Liu, and Blumhardt (2001) examined performance on the PASAT, WCST, and a verbal fluency test in relation to measures of supratentorial gray matter, supratentorial white matter, corpus callosum area, and total cerebral hemisphere volume in a group of 21 RRMS and 20 SPMS individuals and 10 healthy controls. There was a trend of decreased white matter in the overall MS group compared to that in healthy controls, but when individual groups were examined, individuals with SPMS had significantly reduced white matter volumes compared with individuals with RRMS and healthy controls. In addition, the area of the corpus callosum was significantly smaller in both MS groups than in healthy controls. There were significant negative correlations between percentage of white matter and corpus callosum area and performance scores on the WCST and PASAT, although no significant correlations were found for gray matter. Conversely, Morgen et al.'s (2006) examination of gray matter volume in 19 individuals with RRMS showed a significant relationship between gray matter atrophy and PASAT performance. Individuals with low performance on the PASAT had decreased regional gray matter, primarily in the temporal and frontal cortices, while individuals with normal performance on the PASAT did not show regional differences in gray matter. Neither group showed correlations between PASAT performance and white matter volume.

Brain atrophy appears to be a significant contributor to executive dysfunction in MS. Both gray and white matter atrophy can be seen in patients with MS, although greater brain parenchymal reductions are found in patients with more progressive forms of the disease. Though reductions in global and regional white and gray matter volumes have been linked with deficits in executive functioning, the specific influence of these measures to executive impairment is still unclear, possibly due to variations in how brain atrophy is defined and measured and the methodology used to extract and calculate tissue volumes. Additional research should be conducted to address these issues and further shed light on the brain atrophy–executive functioning relationship.

Association with diffusion tensor imaging parameters

In recent years, DTI has become an instrumental tool for quantifying the microstructural damage that occurs in focal white matter lesions and NAWM in individuals with MS. Various methods have been used to examine patterns of whole brain and regional white matter changes in MS, such as tract-based spatial statistics (TBSS) and tractography, with results pointing to compromised white matter in cognitively impaired individuals with MS compared to that in healthy controls and cognitively preserved individuals with MS. Yu et al. (2012), for example, used TBSS to examine the relationship between DTI measures, FA and MD, and performance on the PASAT in 37 individuals with RRMS and 20 healthy controls. Overall, results showed decreased whole brain skeletal FA in individuals with MS compared to that in healthy controls, with regional FA reductions in the

cingulum, fornix, superior fronto-occipital fasciculus, uncinate fasciculus, internal and external capsules, cerebellar peduncle, cerebral peduncle, and corticospinal tract. These reductions in FA corresponded with significantly increased MD in similar regions, which were thought to be driven by increased RD. Correlational analyses further revealed that FA in the sagittal striatum, posterior thalamic radiation, splenium of the corpus callosum, and external capsule was significantly associated with performance on the PASAT.

Additional studies investigating the relationship between executive functioning and DTI measures have found similar results to those of Yu et al. (2012). After controlling for disability, Dineen et al. (2009) found a significant relationship between PASAT performance and FA in the splenium of the corpus callosum, left cingulum, and parietal arc of the left arcuate fasciculus, and Roca et al. (2008) found significant correlations between FA measures in frontolateral regions and PASAT performance in 12 individuals with RRMS compared to healthy controls. The latter study also examined performance on several other executive functioning tests, including "classical" tests, such as the WCST, Trail Making Test, and Digit Span, as well as more specific battery tests, such as the Iowa Gambling Task (IGT), Faux Pas Test (FPT), Hotel Task (HT), and Multiple Errands Test (MET). Overall, there were no significant differences between groups in classical executive functioning tests, but significant differences were found in IGT, MET, and HT performance. Moreover, individuals with MS showed an increased apparent diffusion coefficient (ADC) and decreased FA in frontomedial and frontolateral brain regions, with frontolateral ADC significantly correlating with the number of tasks achieved on the MET and performance on a subtask of the HT. Additional studies examining ADC have linked increased values in the corpus callosum to poor executive performance on the PASAT in individuals with RRMS compared to healthy controls (Lin, Tench, Morgan, Niepel, & Constantinescu, 2005; Lin, Tench, Morgan, & Constantinescu, 2008).

Examinations of MD and diffusivity along (i.e., AD) and perpendicular to (i.e., RD) white matter tracts offer additional information about the microstructure of white matter in MS. Decreases in AD and increases in RD and MD in the inferior longitudinal fasciculus, external capsule, body of the corpus callosum, and corona radiata have been found in individuals with MS and linked to poorer performance on the PASAT (Van Hecke et al., 2010). Moreover, tractography studies focusing on the corpus callosum have found significant associations between RD, AD, and MD and performance on the Trail Making Test, Stroop Color–Word Interference Test, and PASAT (Ozturk et al., 2010; Rimkus et al., 2011). The potential influence of increased MD on executive functioning was also examined by Tovar-Moll et al. (2009) in a study exploring MD and FA in the thalami of 13 RRMS and 11 SPMS individuals and 24 healthy controls. Results showed significant differences in thalamic MD between individuals with SPMS and healthy controls, and correlations were found between thalamic MD for the entire MS group and PASAT performance. No correlations were found for FA.

The aforementioned studies present evidence of a relationship between DTI measures of white matter microstructure and performance on tests of executive functioning. Most of the studies reviewed herein show that compromised white matter, either global or regional, contributes, at least in part, to impairments in executive functioning. A recent study by Genova et al. (2014), however, points to the complexity of this relationship, especially when taking processing speed into account. In their study, 25 MS patients and 15 healthy controls were administered Trials 1–3 of the D-KEFS Color–Word Interference Test (CW) and Trials 2–4 of the D-KEFS Trail Making Test (TMT). Processing speed and executive functioning variables were created for each test, and their relationships with FA were examined. Specifically, the Word Reading and Color Naming subtest scores of the CW were used to create the processing speed factor for the CW test, while the Number Sequencing and Letter Sequencing subtest scores of the TMT were used to create the processing speed factor for the TMT. The Inhibition subtest of the CW and the Switching subtest of the TMT were used as measures of executive functioning. Results showed that processing speed and executive functioning scores on the TMT were independently associated with reduced FA in multiple white matter tracts, but when processing speed was statistically removed from the executive functioning variable, FA was no longer associated with executive functioning on this task. Similarly, processing speed and executive functioning scores

on the CW were independently associated with FA in a number of white matter tracts; however, once processing speed was removed from the CW executive functioning variable, the relationship between reduced FA and executive functioning performance on the CW was reduced to a single tract, the right thalamic radiation. The results of this study suggest that processing speed might play an integral role in certain executive functioning tasks and how they relate to white matter integrity in MS, but it should also be noted that many of the "processing speed" tasks employed in the Genova et al. (2014) study have significant executive components to them, involving rapidly tracking and persisting in a response, and are far from pure processing-speed tasks. The Stroop and D-KEFS Color–Word Interference Test, for example, show moderate to high correlations between word reading/color naming and the inhibition condition (Chafetz & Matthews, 2004; Delis, Kaplan, & Kramer, 2001). As such, studies that examine the mediational effects of processing speed on the relationship between DTI indices and executive functioning may in fact be removing executive functioning from the analysis as much as processing speed. Thus, more research is also needed that includes "processing-speed" tasks that more purely capture the construct and have fewer executive components to them.

DTI has allowed for the examination of microstructural white matter damage in individuals with MS. Recent research has demonstrated that individuals with MS, especially more progressive forms of MS, have more impaired white matter than healthy controls. Decreases in FA and AD and increases in MD, RD, and ADC have been found in persons with MS and linked to executive dysfunction on tests such as the PASAT, TMT, and Stroop Color–Word test. Although more current DTI research points to the role of processing speed in the executive functioning–white matter relationship, further research should be conducted to more "purely" capture processing speed and executive functioning.

Conclusions and future directions

Structural brain damage is a significant consequence of MS. Current research has suggested a significant link between structural brain indices, such as sclerotic lesions, atrophy, damage to NAWM, and executive functioning. Sclerotic lesions, which primarily characterize MS, are commonly found in central white matter and have been shown to contribute to decreased functioning on executive tests such as the WCST and PASAT. Likewise, decreases in gray and white matter volumes have also been linked to poorer functioning on the PASAT and WCST. Yet, although these studies have linked more apparent structural brain damage to executive functioning, the true relationships between these variables are still difficult to ascertain, possibly due to a large variability in methods and measurements. Future research not only should aim to replicate these findings, but should focus on standardizing methods and measurements of lesions and brain atrophy. In addition, more novel techniques, such as DTI, should be used to supplement this research to offer additional insight into the effects of damage outside of lesions and atrophied areas. To date, DTI studies have demonstrated that a relationship between executive functioning and damage to NAWM does exist. Such studies have demonstrated that damage to specific white matter tracts (i.e., corpus callosum, cingulum, corona radiate, etc.) is associated with decreased performance on the PASAT, MET, and the TMT and CW from the D-KEFS. The role of processing speed on executive functioning has also been brought to light. A recent DTI study examining processing speed, executive functioning, and white matter microstructure showed that the relationship between executive functioning and white matter damage was absent when processing speed was accounted for (Genova et al., 2014). It should be noted, however, that it is difficult to separate executive functioning and processing speed, and, therefore, additional research should be conducted looking at processing speed tasks that do not contain large executive components. Lastly, the role of cognitive and brain reserve should be examined as potential influences on the relationship between structural neural correlates and executive functioning.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Primary funding support was from the National Multiple Sclerosis Society [grant number PP1829] (to P.A.A.).

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