Resting-state functional connectivity in multiple sclerosis:
An examination of group differences and individual differences

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ABSTRACT
Multiple sclerosis (MS) is a neurodegenerative, inflammatory disease of the central nervous system, resulting in physical and cognitive disturbances. The goal of the current study was to examine the association between network integrity and composite measures of cognition and disease severity in individuals with relapsing-remitting MS (RRMS), relative to healthy controls. All participants underwent a neuropsychological and neuroimaging session, where resting-state data was collected. Independent component analysis and dual regression were employed to examine network integrity in individuals with MS, relative to healthy controls. The MS sample exhibited less connectivity in the motor and visual networks, relative to healthy controls, after controlling for group differences in gray matter volume. However, no alterations were observed in the frontoparietal, executive control, or default-mode networks, despite previous evidence of altered neuronal patterns during tasks of exogenous processing. Whole-brain, voxel-wise regression analyses with disease severity and processing speed composites were also performed to elucidate the brain–behavior relationship with neuronal network integrity. Individuals with higher levels of disease severity demonstrated reduced intra-network connectivity of the motor network, and the executive control network, while higher disease burden was associated with greater inter-network connectivity between the medial visual network and areas involved in visuomotor learning. Our findings underscore the importance of examining resting-state oscillations in this population, both as a biomarker of disease progression and a potential target for therapeutic intervention.

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1. Introduction

Multiple sclerosis (MS), a chronic, neurodegenerative disease of the central nervous system, has been historically conceptualized as a white matter affliction, with more recent evidence for gray matter degradation. Afflictions of the gray matter typically involve both structural and functional reorganization, in addition to the known white matter damage. The magnitude of neuronal insult observed in MS has been associated with physical, affective, and cognitive impairments, resulting in disability and lower perceived quality of life (see Calabrese, 2006 for review, Devins & Seland, 1987). The impact of this disease on quality of life is further exacerbated by the prolonged burden that most individuals experience as a result of the chronic nature of the disease, with a median age of onset in the mid-thirties and an average disease course of 20–47 years (Kingwell et al., 2012; Visser, Wilde, Yong, Wilson, & Counsell, 2012). Current research on disease-altering therapies to alleviate subjective and objective burden is dominated by pharmacotherapy, often with a focus on physical symptomatology. Although cognitive-focused research in MS has experienced growth over the past ten years, pharmacological and behavior-based treatment options for cognitive impairment are limited, despite a 43–70% prevalence rate of cognitive decline. In our meta-analytic investigation of cognitive impairments in MS, we found evidence for general cognitive impairment in individuals with relapse-remitting MS (RRMS) (g = 0.54), with a large effect size observed for the sub-domain of processing speed (g = 0.646; Prakash, Snook, Lewis, Motl, & Kramer, 2008).

The advent of neuroimaging has contributed substantially to our understanding of the neural correlates of cognitive dysfunction in this population. Alterations in hemodynamic response patterns during tasks of information-processing are present, even in the absence of disease-related cognitive impairment, specifically in areas associated with sensorimotor and executive functioning (Forn et al.,
2. Methods

2.1. Participants

This study was completed as a portion of a larger study that explored the association of protective lifestyle factors with preserved cognitive performance and neuronal plasticity in patients with multiple sclerosis. Participants were recruited from the Columbus, Ohio community via advertisements in the local media and NARCOMS (North American Research Commission on MS), promotional flyers, Research Match (researchmatch.org), and the Multiple Sclerosis Center at the Ohio State University. Participants included in this study were required to have a clinically definite diagnosis of relapsing-remitting multiple sclerosis according to the revised McDonald criteria (Polman et al., 2005), expanded disability-status scale-self report (EDSS) of less than 6, dominant right-handness as indicated by a score of 75% and above on the Edinburgh Handedness Inventory (Oldfield, 1971), between the ages of 30 and 59 years, score greater than 23 on the mini-mental status examination (maximum=30, Folstein, Folstein, & McHugh, 1975), corrected (near and far) visual acuity of 20/40 or better, no use of corticosteroids within the last 30 days, no self-reported history of neurological or any serious psychiatric disorders, absence of depression as indicated by a score of ≤ 18 on the Beck Depression Inventory (Beck, Steer, & Brown, 1996), and no contraindications to the MR environment. Consent to collect protected health information was obtained from the MS participants to verify diagnosis and criteria used, disease duration, and current medications. Demographically-equivalent healthy controls were also recruited for the current study using the above-mentioned criteria. The Ohio State University Institutional Review Board approved the study and all participants provided informed consent.

Twenty-eight healthy control participants met inclusionary criteria for the study. An equal sized sample of MS participants was selected from a larger sample of thirty-three MS individuals that met inclusionary criteria in an effort to equate the two groups on sample size, age, gender, and education; thus ensuring equivalency for various demographic variables and minimizing violating the general linear model’s assumption of equal sample size. The final sample included twenty-eight RRMS participants (mean age=46.4 years, 24 females) and twenty-eight healthy controls, equated for age, education, and gender (mean age=45.6 years, 24 females). Table 1 provides demographic and clinical characteristics for the MS and healthy control samples. As can be seen from the table, the two groups of participants were equivalent with respect to various demographic characteristics.

2.2. Neuropsychological assessment

Prior to the neuropsychological assessment, participants were administered the mini-mental status examination (Folstein et al., 1975) to determine eligibility. To assess functioning in the domain of processing speed, three tasks were chosen from a larger cognitive battery due to their processing speed specificity: the paced auditory serial addition test (PASAT) from Rao’s brief repeatable battery (3 and 2 s. conditions; Rao, 1990); the letter comparison task; and the pattern comparison task from Salihouse (1995). Performance on these tasks was merged to create a composite for processing speed abilities.

2006; Sweet, Rao, Primeau, Mayer, & Cohen, 2004). Targeted investigations of working memory processing, a correlate of processing speed performance, reveal compensatory activation of prefrontal and motor areas during tasks of visual working memory, with the additional activation positively associated with cognitive performance (Sweet et al., 2004; Sweet, Rao, Primeau, Durgerian, & Cohen, 2006).

Extending these task-based investigations of neural recruitment, the study of endogenous processing has the potential to greatly contribute to our understanding of the alterations in the intrinsic functional architecture of the MS brain and its implications for disease progression and cognitive dysfunction. One method of analyzing resting-state data to provide a comprehensive examination of functional insult is to use a network-based approach, providing insight into multiple cognitive systems. Research in healthy young adults has revealed robust and reliable patterns of functional connectivity that exhibit distinct associations with cognitive sub-domains (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006). These patterns have been conceptualized as resting-state networks based on their correlated BOLD signal across a resting-state functional scan and their association with previously identified areas of specialized cognitive functioning. Within the MS literature, the focus of a limited number of resting-state investigations has either been on specific brain networks (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Rocca et al., 2010) or, when comprehensive, whole-head analyses have been employed, (Roosendaal et al., 2010; Rocca et al., 2012) the results have been quite mixed, with neither of these studies examining associations with cognitive performance.

Extending the literature, in the current study, we conducted a parsimonious examination of resting-state network alterations associated with the MS disease course by first examining group-level neuronal network differences in MS individuals relative to healthy controls, and then examining associations between resting-state network integrity and processing speed and disease severity indices. We employed a whole-brain resting-state connectivity approach in the two analyses, thus providing a comprehensive examination of all meaningful resting-state networks that demonstrate reductions as a function of the disease course, as well as all possible network-level associations with the constructs of processing speed and disease severity in one study. The composite measures of processing speed and disease severity were created from multiple examinations of processing speed and disease progression. In the MS literature, several metrics have been employed to quantify disease severity, with the Expanded Disability Status Scale (EDSS) being the most widely used measure (Andersson & Goodkin, 1997). The EDSS, however, focuses primarily on the assessment of ambulatory status and physical decrements and is often correlated poorly with gray matter or white matter damage (Balcer, 2001; Polman & Rudick, 2010). A combination of this measure with an assessment of neuronal insult (T2 lesion load) and a subjective measure of disease burden (disease duration) produces a composite that encompasses multiple aspects of disease-related decline and provides a more parsimonious metric of disease severity. Additionally, we also created a composite measure of processing speed by merging performance on three well-validated tasks of processing speed, thus again, reducing method variance, and providing a more comprehensive metric of processing speed impairment.

Based on the previous research reviewed above, we hypothesized a decrease in overall functional integrity in individuals with MS, negative associations between intra-network neuronal integrity and disease severity, and positive associations between greater network strength and processing speed performance. Specifically, given the ubiquitous declines in motor functioning and impairments in visual processing seen in individuals with MS, we hypothesized loss of functional connectivity in the motor and visual networks. Additionally, given the alterations in patterns of activity seen in exogenously-based functional MRI studies (Forn et al., 2006; Sweet et al., 2004, 2006), we hypothesized MS individuals to show reductions in connectivity of the networks typically involved in attention-based paradigms, including the frontotoparietal networks (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006) executive control network (Zhang & Li, 2012), and the default-mode network, which has more recently been implicated in cognitive control operations (Prakash, Heo, Voss., Patterson, & Kramer, 2012) and which has been shown to exhibit modifications as a result of the disease (Rocca et al., 2010). We predicted the composite of disease severity would be associated with a loss of connectivity, particularly in networks associated with hallmark symptoms of RRMS including motor and visual (Talman et al., 2010; Valasaina et al., 2011; see Frohman, Frohman, Zee, McColl, & Galetta, 2005 for a review). We also expected to observe a positive association between intra-network strength and processing speed performance, specifically in those networks commonly associated with higher-order functioning, including the executive control, default-mode, right and left frontotoparietal, motor, and cerebellar networks (Hawellek et al., 2011).
2.2.1. Paced auditory serial addition test (PASAT)

In this task, participants were auditorily presented with digits at the rate of 2 s per digit (Condition 1) and 3 s per digit (Condition 2). Participants were required to add each digit to the one immediately preceding it and respond verbally with the sum of those two digits. Sixty trials were collected for both conditions, and the number of correctly answered trials was the dependent variable of interest for each condition, respectively.

2.2.2. Letter comparison task

In this task, participants were asked to compare strings of letters of varying set sizes in 60 s. They were presented with sets of 3, 5, 7 or 9 letters on either side of a page, and asked to compare the string on one side of the page to the string on the other and indicate whether those two strings were the same or different by recording an “S” or “D”. The number of correctly identified letter string pairs across two 30-s trials was the dependent variable of interest.

2.2.3. Pattern comparison task

This task was implemented with similar instructions to the letter comparison task, requiring participants to compare single stick patterns presented on either side of the page instead of letter strings. Again, participants were asked to record an “S” or “D” to indicate whether the two patterns were identical or different. The number of correctly identified pattern pairs across two 30-s trials was the dependent variable of interest.

2.3. Functional and structural MRI parameters

Participants were scanned at the Wright Center of Innovation at the Ohio State University campus using a 3T Philips full body scanner. High-resolution structural images were collected for each participant using a 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol with 160 contiguous sagittal slices (TE/TR/TE 3.7/811/1005 ms) collected in an ascending fashion parallel to the anterior and posterior commissures using a spoiled gradient sequence (240 × 240 mm FOV; 1-mm thick slices, with a 1 × 1 × 1 in-plane resolution) with a flip angle of 8 degrees. Sagittal T2-weighted FLAIR images were collected for lesion-load analysis (TR/TE/TI = 11000/3000/1125 and 0.7 × 0.7 × 0.5 mm spatial resolution). Resting-state data was acquired following a fairly standard protocol in which participants were asked to lie down still on the scanner bed, to minimize motion artifacts. Ambient light was minimized, and participants were asked to lie with their eyes open, think of nothing in particular, and not fall asleep (Prakash, Patterson, Jansen, Abduljalil, & Boster, 2011; Smith et al., 2009). These are standard resting-state data collection methods that have been employed in many study protocols, resulting in robust characterization of the functional networks. Scanning parameters for the resting-state scan included T2*-weighted echo planar images (EPI’s) collected with TR/TE 2000/24 ms, flip angle = 80 degrees, 37 slices, 3.44-mm isotropic voxel size acquired within one six-minute functional scan, totaling 180 functional volumes.

2.4. Data Analyses

2.4.1. Processing speed composite

Three tasks from our larger neuropsychological assessment were compiled to create a processing speed composite score, including 2 and 3 s. PASAT conditions, letter comparison, and pattern comparison tasks. Accuracy scores from the four dependent variables were z-standardized and averaged to create a composite processing speed score for each participant. An independent samples t-test was performed to examine group differences and verify sufficient fines of impaired processing speed performance in individuals with RMRS. The composite score was then employed as a continuous variable in whole-brain, voxel-wise regression analysis described below.

2.4.2. Disease severity composite

Three measures of disease progression and severity were collected, including the Expanded Disability Status Scale—self-report, disease duration in years, and T2 lesion load in cubic mm. Self-report EDSS was collected prior to the neuropsychological examination and scored by A.B., a MS neurologist. This measure represents a reliable and valid assessment of disability with an intra-class correlation coefficient of r = 0.89 (Bowen, Gibbons, Gians, & Kraft, 2001). Disease duration information was collected from each participant, and verified by participant’s primary care neurologist after obtaining HIPAA consent and was defined as the number of years since the confirmed diagnosis of MS. T2 lesion load values were calculated for each participant using the methodology described below. The three measures of disease severity were standardized and averaged to create a composite metric of disease severity, thus representing a more comprehensive assessment of each individual’s overall disease burden and a continuous variable for later whole-brain regression analysis.

2.4.3. T2 lesion load analysis

Lesion data was analyzed using T2-weighted, FLAIR images by employing a local thresholding segmentation technique (lim 5.0, Xinapse Systems, www.xinapse.com). This semi-automated segmentation tool is designed to localize white matter hyperintensities based on a template constructed from a representative large sample of MS patients’ scans and detailed empirical knowledge of the likely distribution and size of MS lesions. Lesions were identified manually by placing a marker on the approximate center of each hyperintensity or drawing the approximate border of the sclerotic tissue in the case of widely diffuse hyperintensities along the ventricle border. Next, a fuzzy connectivity algorithm was applied, that extended and mathematically defined the previously manually identified seed regions based on the fuzzy affinity between hyperintense voxels and their neighbors (Udupa & Samarasekera, 1996). The probability weighting value determines how closely each ROI is matched on location and size to the MS lesion template created by the Xinapse research team, while fuzzy connectedness affinity between pixels takes into account the degree of adjacency among voxels, as well as the similarity of their intensity values. Both probability weighting and a fuzzy connectedness threshold was set at 0.25 and 0.62, respectively, based on the fuzzy connectivity algorithm literature (Udupa & Samarasekera, 1996). The result is a new set of algorithm-based regions of interest that encompass the previously manually identified lesions. Two blind raters independently conducted the lesion load analyses using the technique described above. An intra-class correlation alpha of 0.96 was observed for the total lesion load volume.

2.4.4. Resting-state functional connectivity analyses

Resting-state data was analyzed using fMRIB’s software library (FSL; Smith et al., 2004). We first conducted independent component analysis and dual regression to derive subject-specific spatial maps for the networks of interest. We then performed three whole-brain, general linear models to first examine group differences in functional connectivity between individuals with MS and healthy controls. The following two general linear models were conducted on individuals with MS to examine associations of functional connectivity with disease severity and processing speed, respectively.

2.4.4.1. Preprocessing, motion correction, and gray matter density correction

Given the recent publication of studies providing evidence for the influence of motion on functional connectivity magnitude and the possibility of differences in motion p- parameters introducing spurious correlations between groups (Power, Barnes, Snyder, Schlagger, & Petersen, 2012), we implemented a number of procedures to ensure that the observed results represented true differences in connectivity strength between the two groups and were not, instead, driven by motion (Power et al., 2012), gray matter volume (Oakes et al., 2007) or artificial inflation of the BOLD signal as a result of motion and physiological artifacts (Power et al., 2012).

First, we preprocessed our raw EPI data using FMRIB’s linear image registration tool (MCFLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002). This tool involves a default registration to the middle volume and then conducts a coarse 8-mm search followed by two more refined 4-mm searches for relative displacement, and a final tri-linear interpolation optimization. A 3-stage correction process was then carried out based on the mean-image template from previous optimization steps. To further ensure motion was not contributing significant variance to systematic correlations in the functional connectome, we calculated framewise displacement for all our participants (Power et al., 2012). Framewise displacement calculation yielded 6 dimensional timeseries that represented instantaneous head motion and were transformed into a scalar quality via the empirical formula published by Power et al. (2012) As can be seen from Table 1, MS patients and healthy controls were not significantly different from one another in terms of this scalar quantity.

Second, we calculated the framewise change in BOLD signal intensity, commonly referred to as DVARS (Power et al., 2012; Snyder et al., 2010), across the entire brain and examined if there were group-level differences in this metric. Table 1 also presents the mean DVARS for both MS patients and healthy controls. The framewise change in signal intensity was found to be comparable across the two groups, thus ensuring equality between samples on both motion parameters, and intensity changes in BOLD signal that have been found to result in systematic, yet spurious group differences.
Finally, we also controlled for gray matter volume differences between MS patients and healthy controls, as differences in the density of gray matter can contribute to functional connectivity differences. For this, we employed FMRIB’s segmentation tool (FAST; Zhang, Brady, & Smith, 2001) to derive partial volume estimates of gray matter for both MS participants and healthy controls. A common issue in automated segmentation algorithms when applied to a clinical population with white matter hypersintensities, is the misclassification of lesions as gray matter (Sanfilipo, Benedict, Shama, Weinstock-Guttman, & Bakshi, 2005). To alleviate this issue, each MRMS participant’s gray matter probability map was filtered through FSL’s lesion filling algorithm to alter the weighting of the intensity value(s) of the MS lesions on the MPRAGE image by replacing them with values that more closely match those in the non-lesion surrounding area, allowing for the classification of lesions as mainly white matter and not part of the gray matter segmentation map. The finished gray matter segmentations for both groups were then concatenated into two separate 4D files, and utilized as a covariate in the general linear model. This analysis ensured that the functional connectivity differences observed between groups, and as a function of disease severity and cognitive performance, were not driven by differences in gray matter density.

Additional preprocessing steps involved brain extraction using FMRIB’s Brain Extraction Tool (BET; Smith, 2002); spatially smoothing the data using a 5-mm Gaussian smoothing kernel, full width half max (FWHM); temporal band pass filtering using a high-pass filter at 0.08 Hz (125 s.) to remove low frequency scanner drift artifacts; and low-pass temporal filtering at 0.68 Hz (2.68 s.) to remove noise associated with cardiac and respiratory oscillations.

After preprocessing was completed, each subject’s image was first registered to their individual T1-weighted MPRAGE scan, followed by a subsequent registration to Montreal Neurological Institute (MNI) template space using a 12 degree of freedom, affine (linear) transformation. Preprocessed functional data, containing 180 time points for each individual, was concatenated across 56 subjects (28 MS patients, and 28 healthy controls) to create one single 4D dataset, where the fourth dimension represented participants, and then subjected to independent components analysis and dual regression.

2.4.2. Independent component analysis and dual regression. Analyses of within- and between-subject variability in resting-state oscillations were performed utilizing a combined independent component analysis (ICA) and dual regression procedure. ICA, a group network characteristics was conducted first by employ- ing FSL’s multivariate exploratory linear optimized decomposition into inde- pendent components tool (MELODIC; Beckmann & Smith, 2004). The group-ICA decomposed the dataset into 29 components based on the Laplace approximation to the Bayesian evidence for a probabilistic principle component model (Beckmann et al., 2005). The resulting component maps, presented in Fig. 1, were thresholded at a 0.5 probability. Networks of interest were identified based on a correlational matching procedure with previously published, publically available, resting-state templates (Smith et al., 2009). Each of the 29 networks was spatially cross-correlated with the 10 previously identified networks provided in the FSL dataset. Networks were selected first based on highest correlation value with each previously identified FSL network, and then using prior literature to evaluate the structural correspondence of each network with those previously identified by their role in cognitive, sensory, and affective processing. Nine networks of interest were identified as relevant, and each exhibited a correlation coefficient of r ≈ 0.42 or higher with an average correlation coefficient across networks r = 0.61.

Following the identification of networks of interest, a dual regression approach was applied to allow for voxel-wise comparisons of resting-state functional networks between groups. This method employs the full set of group-ICA spatial maps in a linear model fit (spatial regression) against each separate subject’s original 4D resting-state data set. This results in matrices describing the temporal dynamics for each network component and subject. Individual matrices were then variance-normalized and employed in a linear model fit (temporal regression) against each subject’s original 4D data set to estimate subject-specific spatial maps. This analysis produced 29 4D datasets, each representing one original ICA component with the fourth dimension representing all 56 subjects. Each 4D file corresponding to a previously identified network of interest was tested using a voxel-wise general linear model for statistically significant between group differences (Nichols & Holmes, 2002), while controlling for the effects of gray matter density, as described above. After applying this criteria, component maps were then thresholded at z > 2.33, and then corrected for multiple comparisons using Gaussian random field theory at a p = 0.05.

For the nine networks of interest, the two groups were directly contrasted to examine cortical and sub-cortical regions that demonstrated differences in network integration as a result of the MS disease course. Network synchroniza- tion values were extracted from the anatomical peaks of each significant cluster illustrating disease-related functional alteration to provide the statistical z-values along with their anatomical location in cubic mm. Regions of altered connectivity were determined based on statistical peaks in separable anatomical regions as demarcated by the Harvard-Oxford cortical atlas that is packaged with the FSL software package (FSL 4.1.4, FMRIB’s software library, www.fmrib.ox.ac.uk/fsl). 2.4.5. Brain–behavior analyses Correlational analyses with disease severity and cognition were conducted on a whole-brain level utilizing the subject-specific maps from the previous dual regression procedure. Specifically, voxel-wise regression analyses were conducted on the individual-level component maps produced as part of the dual regression procedure, thereby evaluating the network-wide association between neuronal integrity and each continuous variable of interest.

To examine the association of network dynamics in multiple sclerosis with a composite measure of processing speed performance, all 28 participants were included in a linear model regression utilizing the z-standardized composite score values as the predictor and individual-level voxel-wise network integrity values as the dependent variable of interest. Gray matter volume was also included as a covariate in the model to control for the effects of cortical density on functional connectivity alterations. The gray matter masks employed in the present analysis were identical to those utilized and described in the previous group-level comparison analysis. Variables of non-interest, such as age, gender, education, and IQ estimates were not included in the linear model due to their lack of significant association with our composite processing speed measurement. We chose to examine neuronal network change in only those networks previously associated with higher order cognitive functioning, including the executive control, default-mode, left and right frontoparietal, cerebellar, and motor networks. The maps produced from the linear model regression were thresholded at z ≈ 2.33 and corrected for multiple comparisons using Gaussian random field theory at p = 0.05.

We conducted an additional and separate analysis to examine the association between the composite measure of disease severity and individual-level neuronal network integrity. Similar to the previous analysis, this was accomplished using a linear model regression procedure controlling for gray matter density, without the inclusion of any variables of non-interest due to their lack of significant association with our disease severity measurement. This analysis was also conducted on only the 28 individuals with MRMS and all networks of interest. A choice of full network inclusion was made, given the breadth of previous literature suggesting whole-brain level, disease-related alterations across modalities and anatomical regions (Rocca et al., 2012; Roosendaal et al., 2010; Schnoor et al., 2013). We also included both positive and negative association contrasts due to the existing cross-modal theories for compensatory preserved processing (Kern et al., 2012; Loitfelder et al., 2011; Sweet et al., 2004). The resulting maps were thresholded at z = 2.33 and corrected for multiple comparisons using Gaussian random field theory at p = 0.05.

3. Results

3.1. Behavioral results

Table 1 displays group-level statistics of demographic characteristics. Individual samples t-tests were performed to verify the absence of statistically significant differences between MS and healthy controls samples. Demographic variables were not included as covariates in group level imaging analyses, given the reliability of the recruitment matching procedure in producing non-significant group-level demographic differences.

Table 2 presents group level statistics and the results of our independent samples t-test on tasks of processing speed. The composite measure was a compilation of PASAT scores on 2 and 3 s. conditions, pattern and letter comparison tasks. Consistent with previous research, MS participants scored significantly lower on the processing speed composite, relative to health controls (t = –3.49, p < .01).

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<th>MS</th>
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<td>Composite</td>
<td>–0.3 (0.7)</td>
<td>0.3 (0.7)</td>
<td>–3.49</td>
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<td>Pattern comparison</td>
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<td>38.6 (5.7)</td>
<td>–1.345</td>
<td>0.15</td>
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<tr>
<td>Letter comparison</td>
<td>21.5 (4.4)</td>
<td>24.8 (5.3)</td>
<td>–3.318</td>
<td>0.001</td>
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<tr>
<td>PASAT 2s</td>
<td>30.2 (12.2)</td>
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<td>PASAT 3s</td>
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3.2. Imaging results

3.2.1. ICA results

A group-level independent component analysis (ICA) yielded nine networks of interest, which were identified through spatial cross-correlation and reference to previous literature. A visual depiction of these networks can be found in Fig. 1. The identified networks included:

- The default-mode network (DMN) (a), which consists of the precuneus, posterior cingulate cortex, ventro-medial prefrontal cortex, lateral parietal cortices, and bilateral hippocampi. The DMN is a widely studied resting-state network and commonly seen as deactivating in task-based fMRI experiments designed to tap cognitive control abilities. While the function of DMN still remains elusive, this network exhibits strong anti-correlations with task-positive networks implicated in cognitive control (Uddin, Kelly, Biswal, Castellanos, & Milham, 2009; Buckner, Andrews-Hanna, & Schacter, 2008), and has exhibited empirical associations between intact functional integrity and preserved cognitive functioning in MS and healthy control populations (Hawellek et al., 2011).

- The executive control network (b) includes the anterior cingulate and paracingulate cortex, bilateral inferior and superior frontal gyri, and bilateral angular gyri. Previous research implicates these areas in cognitive paradigms involving executive functioning, action inhibition, and decision-making (Cannon, Congedo, Lubar, & Hutchens, 2009; O’Doherty & Bossaerts, 2008; Zhang & Li, 2012). Additional investigations of working memory impairment in RRMS have also exhibited...
structural and functional changes within many of these areas (Li et al., 2004; Sweet et al., 2004).

- The motor network (c) incorporates the bilateral supplementary motor areas, sensorimotor cortex, and secondary somatosensory cortex. Multiple paradigms of bilateral motor movement provide evidence for the involvement of this network in both proximal and distal movements. Motor and somatosensory areas have also been implicated during tasks of bilateral and ipsilateral finger movements, motor learning, and motor imagery (Grafton, Woods, & Mazziotta, 1993; Kim et al., 1993; Lowe et al., 2002; Porro et al., 2002), implicating this network in movement-related cognition, as well as motor execution.

- The cerebellar network (d) consists of the cerebellum and areas of the thalamus. Previous research provides support for the involvement of this network in motor action-execution and perception paradigms (Penhune & Steele, 2012). A more recent meta-analytic investigation provides evidence for cerebellar involvement in higher-order cognitive domains such as emotion, sensory perception, timing, language, working memory, and music (E. Chen, Ho, & Desmond, 2012). A targeted analysis of individual lobe and hemispheric connectivity within specific regions of the cerebellum has linked the anterior cerebellum with areas of the motor system, while the posterior cerebellum appears to be more functionally connected to higher-order cognitive networks including executive control, left and right frontoparietal, and default mode network (Bernard et al., 2012).

- The medial visual network (e) subsumes many early visual processing areas including occipital pole, cuneus, and areas of the precuneus. These areas comprise V1 and V2 visual cortex involved in early line orientation and color distinction (Rosa et al., 2009; Tootell et al., 1998). More specifically, activation in the central part of the occipital lobe corresponds to cognition-language-orthography paradigms, (Gitelman, Nobre, Sonny, Parrish, & Mesulam, 2005; McCandliss, Cohen, & Dehaene, 2003), supporting the role of medial visual areas in early visual processing and stimuli identification. This network has also been implicated in visuomotor learning paradigms, incorporating higher-order processing areas to complete visual tasks of increasing complexity (see Culham, He, Dukeleto, & Verstraten, 2001 for a review). Tables 3-4

- The lateral visual network (f) encompasses higher-order visual processing areas including bilateral lateral occipital cortices, bilateral occipital fusiform gyri, and parts of the occipito-temporal junction. These areas were originally associated with motion processing and visual attention (Moran & Desimone, 1985). However, more recent findings have also linked lateral visual processing areas to cognition-space paradigms involving visual integration from retinotopic visual fields to egocentric frames useful in executive processes (Domagali, Beldzik, Fafrowicz, Oginska, & Marek, 2012).

- The left and right frontoparietal networks (g & h), which display lateralization to their respective hemispheres, include the lateral occipital cortices, inferior parietal cortices, middle and superior frontal gyri, and intraparietal sulci. Both networks are involved during several higher-order cognitive operations. Specifically, the left frontoparietal displays a functional association with language processing, as well as visual working memory, attention, and episodic memory retrieval (Coul, Frith, Frackowiak, & Grasby, 1996; Lidaka, Sadato, Yamada, & Yonekura, 2001; Ostby, Tamnes, Fjell, & Walhovd, 2011; Ray, Mackay, Harmer, & Crow, 2008). The right frontoparietal network is more involved with sensory perception and pain, as well as spatial attention and cognitive control (Coul et al., 1996; Fassbender et al., 2006; Walter & Dassonville, 2011). Both networks are imperative to successful attentional allocation and executive functioning demands.

- The auditory network (i) includes superior temporal gyrus, Heschl’s gyrus, and posterior insula, corresponding most strongly with speech execution, language paradigms and auditory perception (see Hackett, 2011 for review).

3.2.2. Group differences in resting-state connectivity

Fig. 2 and Table 3 illustrates group differences in three of the nine networks of interest. Overall, our results provide evidence for altered patterns of functional connectivity in MS patients, relative to healthy controls, across a number of networks linked to specific modalities that exhibit decline as a function of the RRMS diagnosis. Networks showing differential patterns of synchronization included:

Motor network. Somato-motor impairments are considered to be the hallmark symptoms of MS, often noted early in the disease course and providing explanatory variance to a variety of other cognitive impairments. In a seminal study of resting-state connectivity, Lowe et al. (2002) observed reduced low-frequency coherence between bilateral areas of motor cortices in MS individuals, thus providing the first evidence for altered patterns of functional connectivity within this population. Several studies since have corroborated the initial examination of reduced functional connectivity in the motor cortex in individuals with MS. In this study, we found lower intra-network connectivity values in the right primary motor cortex (M1), left somatosensory cortex, specifically S1, the right supplementary motor cortex, and the left anterior supramarginal gyrus in individuals with MS (Fig. 2). These areas are involved in movement execution and planning, sensory processing, and motor-learning paradigms and have been noted for their significant association with disability (Bensmaia & Yau, 2011; Filippi et al., 2003; Reddy et al., 2002) and putative role in disease-related functional alterations during motor tasks early in the disease course.

Medial and lateral visual networks. Reductions in synchronization were also observed in MS patients in the two visual networks, corroborating previous findings of significant impairments in the visual abilities of individuals with MS (Ebers, 1985). Healthy controls displayed greater connectivity in the medial visual
network, specifically in the right intracalcerine cortex, right superior lateral occipital cortex, left precuneus cortex, left lingual gyrus and left VI lobule of the cerebellum. A recent investigation of homotopic resting-state functional changes corroborates these findings, illustrating similar decreased intra-hemispheric functional connectivity values in the primary visual cortex (Zhou et al., 2013). RRMS individuals also exhibited functional alterations in the lateral visual network, including secondary visual cortices. Lower network strength values were noted in bilateral inferior lateral occipital cortex, right superior lateral occipital cortex, and bilateral occipital poles, all regions previously identified as functionally altered displaying decreased intra-network integrity in patients with and without a history of optic neuritis (Gallo et al., 2012).

3.2.3. Brain–behavioral associations

Fig. 3 and Table 4 illustrates whole-brain level associations with disease severity. A negative association between disease severity and functional connectivity of the motor network was observed, such that a higher level of disease burden was associated with reduced connectivity of the left motor cortex and premotor areas. This result substantiates previous investigations of connectivity loss as a function of the MS disease course in the motor network (Lowe et al., 2002; Rocca et al., 2010; Roosendaal et al., 2010). However, to our knowledge, this is the first finding to link the decrease in functional intra-network connectivity to an increase in disease severity, despite a breadth of evidence indicating motoric disability as the primary degenerating symptom in the majority of RRMS individuals (Lauer & Firnhaber, 1992; Pelletier et al., 2001; Yozbatiran, Baskurt, Baskurt, Ozakbas, & Idiman, 2006).

Disease severity was also negatively associated with functional connectivity of the executive control network such that greater disease progression was associated with lower functional intra-network integration of the right inferior frontal gyrus and right frontal orbital cortex. The association of less functional connectivity in regions typically associated with the executive control network and an increase in disease severity is indicative of neuronal-level insult to higher-order cognitive functioning regions, despite the absence of an association with processing speed performance. Previous investigations of executive functioning and attention, both domains that involve executive control network regions, also exhibited reduced connectivity of the right IFG during task, both early and late in the disease course (Forn et al., 2007, 2012; Nebel et al., 2007).

Table 4
Brain–behavior analysis results of whole-brain disease severity regression analysis for the three networks that exhibited significant associations. Medial visual network was found to be positively associated with disease severity, while executive control and motor networks were found to be negatively associated with disease severity. Coordinates are reported in mm in Montreal Neurological Institute (MNI) space.

<table>
<thead>
<tr>
<th>Disease severity associated networks</th>
<th>Coordinates</th>
<th>Peak z-stat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial visual network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior cingulate cortex</td>
<td>10 38 8</td>
<td>3.64</td>
</tr>
<tr>
<td>Left pallidum</td>
<td>–22 –6 0</td>
<td>3.71</td>
</tr>
<tr>
<td>Left putamen</td>
<td>–26 –2 14</td>
<td>3.79</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>34 38 –16</td>
<td>3.52</td>
</tr>
<tr>
<td><strong>Executive control network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>42 34 0</td>
<td>4.12</td>
</tr>
<tr>
<td>Right frontal orbital cortex</td>
<td>42 30 –4</td>
<td>3.85</td>
</tr>
<tr>
<td><strong>Motor network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left primary motor cortex</td>
<td>–38 2 36</td>
<td>3.47</td>
</tr>
</tbody>
</table>
We also found evidence for medial visual network integrity to be positively associated with disease severity in regions that are typically implicated in visuomotor learning paradigms, including the right anterior cingulate cortex, left pallidum, left putamen, and right inferior frontal gyrus (Seidler, Noll, & Chintalapati, 2006; Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001). Similar network-level findings of greater integration between executive control regions and primary visual cortex were also observed in previous resting-state investigations within the MS population (Rocca et al., 2012).

Finally, we conducted a separate whole-brain level analysis to examine associations of processing speed with our chosen networks of interest. Surprisingly, we did not find our composite measure of processing speed to be associated with connectivity strength in any of the examined networks.

4. Discussion

The implication of functional brain alterations for disease progression, cognitive deficits, and overall quality of life in the MS population has become a topic of great interest in the MS community. Despite unequivocal evidence of an association between disease-related symptomatology and quality of life (Amato, Ponziani, Siracusa, & Sorbi, 2001; Auty et al., 1998), there is a dearth of brain–behavior literature associating disease progression and cognitive decline with network dynamics on a whole-brain level. Over the past few years, multiple studies have sought to explain the change in network organization as a function of MS (Rocca et al., 2012; Roosendaal et al., 2010), but without further extension to whole-brain level disease severity and cognitive performance associations, which would be necessary for a more complete understanding of the qualitative nature of network-level alterations in the MS population. Extending the scope of previous investigations and clarifying prior discrepancies in MS-related network alterations, the current study included whole-brain level associations between network dynamics and composite measures of cognition, specifically targeting processing speed deficits and disease severity. An ICA and dual-regression based approach was employed to examine the fluctuations in network dynamics as a function of the MS disease course, overall disease burden, and the commonly associated deficits of processing speed, while controlling for gray matter density. Our results provide evidence of network-level alterations in individuals with MS in the motor and visual networks, with no reductions in the connectivity of the networks typically implicated in cognitive control operations. Additionally, a negative association between disease severity and network alterations was also observed in the MS population, suggesting differential resting-state connectivity as a function of disease burden.

Our study provides evidence for reduction in the connectivity of the motor network in individuals with MS, corroborating previous investigations of resting-state alterations in this network in RRMS patients (Lowe et al., 2002; Roosendaal et al., 2010). We observed less functional integrity in the left somatosensory cortex, specifically the S1 region, right primary motor cortex (M1), right supplementary motor cortex, and left anterior supramarginal gyrus within the motor network, a network typically associated with disease severity. The analysis was completed on the 28-person RRMS dataset, utilizing the individual-level network maps produced from the dual regression analysis for group-level network comparison. Network maps were thresholded at $z=2.33$ and $p=0.05$ and displayed in the radiological convention.

**Fig. 3.** Whole-brain level, voxel-wise regression analysis of disease severity associations with network integrity. The analysis was completed on the 28-person RRMS dataset, utilizing the individual-level network maps produced from the dual regression analysis for group-level network comparison. Network maps were thresholded at $z=2.33$ and $p=0.05$ and displayed in the radiological convention.
with movement planning and execution, sensory processing, and motor learning. Less integration of these widespread motor and sensory regions within the motor network as a whole further validates previous findings of the reorganization of sensorimotor regions during task-based activation studies as a function of the MS disease course (Dell’Acqua et al., 2010; Valsasina et al., 2011). Further, a negative association between functional integrity in the left primary motor cortex and disease severity provides the first evidence of its kind to link network-level resting-state alterations in the motor cortex with disease burden. Previous studies reporting an association between structural reorganization in the somatomotor cortex and disease severity have found so only in the progressive sub-types of this disease (Loitfelder et al., 2011). Examining neural recruitment during a motor task, Reddy et al. (2002) found evidence for differential neural recruitment in the ipsilateral premotor cortex and supplementary area to be associated with brain injury load (Reddy et al., 2002). Corroborating this study of exogenous-based processing, our finding of less left primary motor cortex connectivity as a function of greater disease burden in right-handed MS individuals provides evidence for progressive degenerating changes in intrinsic network connectivity of the motor network in this population. Given the ubiquitous decline in activity and connectivity of the motor network, along with accompanying motor performance deficits in this population, future research endeavors would add to the existing literature through a longitudinal examination of the link between motor network alterations and disease progression within this population. An interesting line of research would be to follow individuals diagnosed with clinically isolated syndrome suggestive of multiple sclerosis (CISSMS) and examine if alterations in the motor network at baseline are predictive of conversion from CISSMS to clinically-definite MS.

We also found evidence for less functional integrity of the medial visual network in RRMS patients, relative to healthy controls. Less connectivity was observed in areas of the primary visual cortex, including the right intracalcarine cortex, right superior lateral occipital cortex, left precuneus cortex, left lingual gyrus, and left lobule VI of the cerebellum. These regions are typically involved in early visual processing and implicated in previous resting-state network investigations of the visual cortex in healthy young adult populations (Chawla, Rees, & Friston, 1999; Sang et al., 2012). A targeted investigation of visual network asynchrony during resting-state in RRMS individuals exhibited similar results of functional loss in the V1 cortex in patients with and without a history of optic neuritis (Gallo et al., 2012), ruling out the role of optic nerve degeneration in V1 dysfunction. A more recent examination of inter-hemispheric, homotopic functional organization has also substantiated the loss of connectivity between right and left primary visual cortex in RRMS, providing further evidence for functional network alteration (Zhou et al., 2013). Behavioral correlates of medial visual network function, including visual acuity and contrast sensitivity, both exhibit decline as a function of the MS disease course and have been positively associated with performance on visual, non-visual, and motor-based neuropsychological tests (Feaster & Bruce, 2011). The presence of both progressive behavioral decline and functional network alterations suggests that medial visual network disintegration is likely symptomatic and possibly associated with disease progression. Previous investigations have linked disease severity measurements, such as EDSS and T2 lesion load, measurements typically associated with V1 cortex processing and performance on non-visual, motor-based neuropsychological tests, to poorer visual acuity and contrast sensitivity, but have neglected to examine the involvement of primary visual cortex functioning (Feaster & Bruce, 2011; Wu et al., 2013). The results of the current investigation provide a missing link between medial visual network alteration and disease burden, specifically, in the positive association of disease progression measures with greater inter-network connectivity of cortical and subcortical regions not typically associated with the spatial configuration of the medial visual network. More precisely, higher levels of disease severity were associated with greater connectivity between the medial visual network and areas implicated in visuomotor learning paradigms, such as the anterior cingulate cortex, inferior frontal gyrus, pallidum and putamen (Seidler et al., 2006; Toni et al., 2001). Short-term, single session visuomotor learning paradigms have substantiated the presence of impaired learning performance associated with these specific regions in multiple sclerosis (Bonzano et al., 2011; Tomassini et al., 2012). However, longitudinal investigations that allow for learning to take place over repeated trials exhibit no impairments at follow-up and provide further support for compensatory brain plasticity as a function of the MS diagnosis (Tomassini et al., 2012). In a recent investigation by Tomassini et al. (2012), fMRI data was collected on a visuomotor learning task during its first introduction to the participants, where significant impairment in performance was observed, and after 2 weeks of practice, where MS patients later elicited similar visuomotor learning gains as healthy controls, illustrating non-significant performance differences at time 2. Interestingly, task-based activation patterns after two-weeks of practice exhibited smaller activation reductions of primary visual areas, indicating a compensatory lack of medial visual network deactivation necessary for preserved visuomotor learning performance. The findings of the current investigation suggest that the compensatory lack of medial visual deactivation during acquired visuomotor learning is indicative of less functional uncoupling during rest of normally segregated networks. Similar findings of less network segregation between executive control and medial visual networks have been previously substantiated, but not related to the progression of the disease course (Rocca et al., 2012). This study is the first to associate compensatory resting-state coupling of medial visual and visuomotor regions to disease progression, such that the strength of the functional relationship between brain regions increases with disease progression. Similar to the increased intra-network coherency observed in this study, other studies within the MS population have linked compensatory brain plasticity alterations in the motor cortex and serotogenic transmission within the visual system with disease progression (Pantano et al., 2002; Sandyk, 1999), substantiating the validity of the current implications. Future investigations could further elucidate this finding through longitudinal examinations of visuomotor learning across the disease spectrum. Our findings suggest that compensatory coupling of medial visual and visuomotor learning regions during preserved visuomotor learning performance increases with disease progression, but it would be important to further explore the functional ramifications of this intra-network coherency both for tasks of visual acuity and sensitivity as well as for visuomotor learning paradigms.

Visual network integrity differences were also observed in the lateral portion of the occipital lobe, a finding that has been replicated previously in patients with and without a history of optic neuritis (Gallo et al., 2012). Evidence from a study of patients with optic neuritis linked early neuroplasticity in areas of the lateral occipital complex with greater levels of vision recovery at 12-month follow-up (Jenkins et al., 2010), supporting the presence of less functional integrity in the lateral visual network and its association with optic nerve insult. Vision-related deficits can also be observed earlier in the visual system at the level of the retinal nerve fiber layer (Herrero et al., 2012), and optic pathways (Evangelou, Konz, & Esiri, 2001), suggesting that the current findings might not be a product of true visual network reorganization, but a function of visual system disruption earlier in the sensory stream. Although previous investigations have failed to find network level alterations in the lateral
visual network, the evidence of decreased functional integrity in previous targeted visual network investigations (Gallo et al., 2012) and the robust evidence for primary and secondary visual impairments (see Sakai, Feller, Galetta, Galetta, & Balcer, 2011 for a review) aid in substantiating the presence of less functional integration within the lateral visual network. Future investigations would be prudent to examine the contributing variance of early visual system insult to lateral visual network integration to further define the presence of true network reorganization.

Although no group-level differences were exhibited, regions of the executive control network (ECN), including the right inferior frontal gyrus and right frontal orbital cortex, exhibited negative associations with disease severity such that disease progression, as measured by our composite scale, was associated with less intra-network connectivity of the ECN. Task-based investigations of executive processing typically associated with ECN regions have also illustrated reduced connectivity of inferior frontal gyri and frontal orbital cortices during working memory (Au Duong et al., 2005), as well as reduced activation during executive attention (Nebel et al., 2007) and inhibition tasks (Bonnet et al., 2010), all of which represent primary executive control domains (Miyake, Friedman, Emerson, Witzki, & Howarter, 2000). A prior investigation by Rocca et al. (2012) illustrated a similar negative association between executive control intra-network IFG connectivity and T2 lesion load, but not EDSS. The current results provide additional explanatory variance that links T2 lesion load, EDSS, and disease severity using a more comprehensive measure of neuronal, physical, and duration-related insult, to lower ECN intra-network integrity.

The lack of significant correlation between network strength and a composite measure of processing speed was surprising. Given that impediments in processing speed are considered to underlie deficits in higher-order cognitive impairments (De Luca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004), we had hypothesized processing speed deficits to be negatively associated with functional connectivity of networks implicated in higher-order cognitive control operations. This hypothesis was also based on evidence from studies of exogenous processing that have illustrated significant alterations in the activity of the frontal and parietal regions during tasks of processing speed (Genova, Hillary, & Glenn, 2009; Leavitt, Glenn, & Genova, 2012). It is likely that, despite declines in processing speed, both behaviorally and during exogenous-based neural activity, processing speed measures are not correlated with the spontaneous fluctuations in intrinsic activity. Also, in our study, we chose to employ processing speed as a dimensional construct, and it might be important in future studies to classify MS individuals into cognitively-preserved and cognitively-impaired subgroups utilizing population-based norms to examine differential connectivity as a function of cognitive impairment.

The current study reflects a comprehensive examination of functional network integrity in individuals with RRMS. The behavioral ramifications of network alteration were examined through a whole-brain, network-level regression association with comprehensive measures of cognition and disease severity that were able to encompass more variability than any one measure alone. While findings did support significantly lower functional connectivity values in three networks of interest in MS individuals, we failed to find associations between functional integrity and processing speed composite scores. Correlations with cognitive performance could benefit from the inclusion of a measure that would separate cognitively-impaired from cognitively-preserved individuals by providing a behavioral moderator for network alterations, as has been previously substantiated within the default mode network (Rocca et al., 2010). An additional limitation of our study was the targeted analysis of processing speed. There is a possibility that additional cognitive domains, not dependent on processing speed, could also be affected and exhibit differential network associations as part of the disease course. Future investigations of the association between network-level alterations and higher-order executive control tasks including working memory, action inhibition, and set-shifting would be necessary to further understand the associations between cognitive functioning and related network-level modulations.

Overall, the current investigation contributes to the existing literature by elucidating the role of inter- and intra-network dynamics in cognitive processing and disease progression within the RRMS population, relative to a healthy control group, while controlling for the possible confounding effects of gray matter density. Specifically, this investigation verifies the presence of less intra-network connectivity in RRMS patients across, motor, medial visual, and lateral visual networks relative to healthy controls. Despite the lack of associated network alterations with processing speed performance, significant positive and negative associations with disease severity were observed in the medial visual, executive control, and motor networks. Our results provide support for the further study of resting-state oscillations within this population, both as a biomarker of disease progression, as well as a target outcome for future therapeutic interventions. An interesting line of future research would be to investigate functional reorganization in the intrinsic architecture of the brain when individuals are first diagnosed with clinically isolated syndrome suggestive of multiple sclerosis (CISSMS) and follow them longitudinally to examine if, firstly, network alterations are present in this prodromal phase of the disease, and secondly, if network alterations at baseline are predictive of conversion to the clinically-definite MS (CDMS). The use of techniques like multi-voxel pattern analysis (MVPA) that take advantage of the functional and structural connectome to predict conversion to CDMS, and subsequent cognitive impairment has the potential to further the study of MS and possibly contribute to the design of interventions that will either help preserve the functional integrity of the brain or capitalize on intra-network connectivity to improve behavioral performance.

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References
