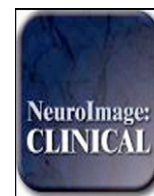


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Intra-individual variability in information processing speed reflects white matter microstructure in multiple sclerosis

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ABSTRACT

Slowed information processing speed is commonly reported in persons with multiple sclerosis (MS), and is typically investigated using clinical neuropsychological tests, which provide sensitive indices of mean-level information processing speed. However, recent studies have demonstrated that within-person variability or intra-individual variability (IIV) in information processing speed may be a more sensitive indicator of neurologic status than mean-level performance on clinical tests. We evaluated the neural basis of increased IIV in mildly affected relapsing–remitting MS patients by characterizing the relation between IIV (controlling for mean-level performance) and white matter integrity using diffusion tensor imaging (DTI). Twenty women with relapsing–remitting MS and 20 matched control participants completed the Computerized Test of Information Processing (CTIP), from which both mean response time and IIV were calculated. Other clinical measures of information processing speed were also collected. Relations between IIV on the CTIP and DTI metrics of white matter microstructure were evaluated using tract-based spatial statistics. We observed slower and more variable responses on the CTIP in MS patients relative to controls. Significant relations between white matter microstructure and IIV were observed for MS patients. Increased IIV was associated with reduced integrity in more white matter tracts than was slowed information processing speed as measured by either mean CTIP response time or other neuropsychological test scores. Thus, despite the common use of mean-level performance as an index of cognitive dysfunction in MS, IIV may be more sensitive to the overall burden of white matter disease at the microstructural level. Furthermore, our study highlights the potential value of considering within-person fluctuations, in addition to mean-level performance, for uncovering brain–behavior relationships in neurologic disorders with widespread white matter pathology.

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1. Introduction

1.1. Information processing in multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system that is associated with neurologic and cognitive impairments (e.g., (Keegan and Noseworthy, 2002)) that result in extensive societal burden (Canadian Institute of Health Information,

2007). Cognitive dysfunction affects approximately 40–65% of MS patients (Chiaravalloti and DeLuca, 2008; Hoffman et al., 2007; Patti et al., 2009). Reduced information processing speed is the most frequently reported impairment and has been hypothesized to contribute to dysfunction of higher order cognitive abilities such as working memory and executive functions (DeLuca et al., 2004; Tombaugh et al., 2010). Information processing speed in MS is typically evaluated on the basis of performance accuracy on speeded clinical neuropsychological tests. In particular, the Paced Auditory Serial Addition Test (PASAT (Gronwell, 1977)) and the Symbol Digit Modalities Test (SDMT (Smith, 1982)) are widely employed in both clinical and research settings, due to their high sensitivity to dysfunction (Brochet et al., 2008; Drake et al., 2010; Hayton et al., 2012; Rovaris et al., 1998; Snyder and Cappelleri, 2001). Recently, computerized tasks that measure reaction time have also been employed in MS research with greater frequency (Reicker et al., 2007; Tombaugh et al., 2010; Wojtowicz et al., 2012a). Poor performance, as measured by a reduced number of correct responses or slower mean reaction time, is inferred to reflect slowed information processing.

Abbreviations: CTIP, Computerized Test of Information Processing; IIV, intra-individual variability.

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1.2. Intra-individual variability

In addition to the total number of correct responses within a given time period or the mean-level reaction time for a speeded task, intra-individual variability (IIV) on trials within timed tests of information processing speed also provides insight into patients' cognitive functioning. To understand how IIV can provide additional information unique from mean-level performance, consider the following example of two patients with equally slowed mean-level performance. One patient's performance might be consistently slowed on all trials, with approximately the same IIV as healthy controls. The other patient's responses might be more widely distributed, with both normal and slow trials contributing to the overall slowed performance such that IIV is increased. In this way, IIV can provide insight into performance differences over and above mean-level measures.

Greater variability in response speed across trials within a task has been demonstrated in populations with various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, mild cognitive disorders, dementia, traumatic brain injury, schizophrenia, and attention deficit and hyperactivity disorder (Anstey et al., 2007; Burton et al., 2002; Hultsch et al., 2000; Li et al., 2001; MacDonald et al., 2006; MacDonald et al., 2009; Manoach, 2003; Murtha et al., 2002). Recently, relapsing–remitting MS patients have been found to demonstrate greater IIV in performance compared to healthy controls, even when potential sensorimotor confounds were controlled (Wojtowicz et al., 2012a). IIV has also been found to better discriminate MS patients from healthy controls in comparison to mean response time or level of performance on common clinical tests such as the PASAT (Bodling et al., 2012; Wojtowicz et al., 2012a; Wojtowicz et al., 2013). Thus, previous research has shown that IIV provides unique information regarding information processing difficulties in MS. However, while IIV is known to be associated with decreased white matter volume (Walhovd and Fjell, 2007) and integrity (Fjell et al., 2011) in healthy individuals, the relation between IIV and white matter integrity of MS patients has not yet been demonstrated. Understanding the neural basis of increased IIV in MS could provide important insights into the cause of this important source of disability and provide sensitive indicators of disease progression.

1.3. White matter integrity in MS: diffusion tensor imaging

Diffusion tensor imaging (DTI) has emerged as a key MRI methodology for understanding white matter pathology in MS (e.g., (Rovaris et al., 2005)). Studies have consistently reported differences in DTI metrics between MS patients and controls, such as decreased fractional anisotropy (FA) within the normal appearing white matter of patients (NAWM; e.g., (Hasan et al., 2005; Roosendaal et al., 2009)), reflecting decreased integrity of white matter tracts (Kochunov et al., 2009; Le Bihan and Johansen-Berg, 2012). DTI appears more sensitive to disease-related phenomena than lesion burden as seen on conventional MRI, and relations between DTI metrics and information processing speed in MS patients have begun to emerge in the recent literature (e.g., (Dineen et al., 2009; Kern et al., 2011; Yu et al., 2012)). For example, Yu et al. (2012) reported correlations between reduced FA and impairment on multiple clinical neuropsychological tests, with the strongest correlations observed for the SDMT. However, to date only mean-level information processing speed has been evaluated in relation to DTI.

1.4. Study objectives

The main objective of the current study was to explore the neural basis for increased IIV in MS and in particular, its association with white matter microstructure. We hypothesized that, in a sample of mildly affected MS patients, IIV would be significantly related to white matter integrity. Given recent behavioral evidence that IIV

better discriminates between MS patients and controls than mean reaction time (Bodling et al., 2012; Wojtowicz et al., 2012a; Wojtowicz et al., 2013), we further hypothesized that IIV would be more sensitive to white matter microstructure than would mean reaction time in MS patients. In addition to mean reaction time and IIV on timed tests, we also examined MS patients' performance on the SDMT, a commonly used clinical test of information processing speed. As well, we examined conventional MRI measures of lesion burden and whole brain atrophy among MS patients.

2. Material and methods

2.1. Participants

All participants provided informed consent and were compensated for participation following procedures approved by the Capital District Health Authority Research Ethics Board in compliance with the Declaration of Helsinki. Twenty female participants with clinically definite relapsing–remitting MS (Polman et al., 2011) were recruited from the Dalhousie MS Research Unit, at the time of their scheduled visits to this specialized clinic for MS care. All had been clinically stable, had not taken corticosteroids for at least three months, and had no more than moderate neurologic disability as assessed by the Expanded Disability Status Scale (i.e., EDSS scores between 0 and 6 (Kurtzke, 1983)). All MS participants were receiving first-line disease modifying therapy for treatment of MS at the time of the study (O'Connor and Devonshire, 2008). None had comorbid neurologic or psychiatric disorders. Other exclusion criteria were a history of substance abuse, learning disability, head trauma, or seizures. MS participants with a history of depression or anxiety disorders were included only if it was not an active clinical problem at the time of the study, as determined by MS clinic staff. Twenty control participants, matched for sex, age, and education, were recruited from advertisements and word of mouth. The same inclusion and exclusion criteria were applied to the healthy participant group except for those related to MS. All participants reported normal or corrected-to-normal vision at the time of the study.

2.2. Behavioral data

For behavioral data, group comparisons (two-sample *t*-tests) and correlations within the MS participant group (controlling for age) were performed in SPSS Version 20.0 (IBM Corporation, 2011). For *t*-tests in which the assumption of homogeneity of variance was not met, Levine's correction was applied.

2.2.1. Clinical measures

EDSS scores were obtained from the MS patients' medical records, with all clinic visits occurring within two weeks of their participation in the study. All participants completed the oral version of the SDMT (Smith, 1982), a clinical test of information processing speed. To assess whether symptoms of depression were a confounding issue, participants also completed the Beck Depression Inventory–Fast Screen (Beck et al., 2000).

2.2.2. CTIP

2.2.2.1. Administration. The Computerized Test of Information Processing (CTIP) (Tombaugh and Rees, 2008) was used to evaluate both mean response speed and IIV. IIV on the CTIP has been previously shown to better discriminate MS patients from healthy controls than mean response speed (e.g., (Wojtowicz et al., 2012a)). Participants performed the CTIP in a quiet testing room on a 15" Apple MacBook Pro. The CTIP includes three reaction time subtests that progressively increase in complexity and cognitive processing demands: 1) a simple reaction time (SRT) task in which participants are asked to press the spacebar as soon as an "X" appears on the screen; 2) a

choice reaction time (CRT) task in which participants are asked to press the right key (i.e., “/”) or the left key (i.e., “z”) when they see the words “DUCK” or “KITE,” respectively; and 3) a semantic search reaction time (SSRT) task in which participants are asked to decide if a given word belongs to a particular category. On each trial of the SSRT, one of four semantic categories is presented at random (Weapon, Furniture, Bird, or Fruit). Two seconds later, a word appears below the category. The participants are asked to press the right key if the word belongs to the category and the left key otherwise. Each task includes 10 practice trials and 30 test trials, for a total duration of 10–15 min.

2.2.2.2. Analysis. Trials with incorrect responses were excluded from all analyses. Mean reaction time was calculated for each participant for each CTIP subtest. IIV was calculated as the individual standard deviation (ISD) (Wojtowicz et al., 2012a). This measure controls for systematic factors that can affect variability (e.g., practice, learning effects) and ensures that differences in variability are not a statistical artifact of differences in individual or group mean performance (Hultsch et al., 2000). Such undesirable effects are parceled out using regression and the standardized residual scores are transformed to *t*-scores to calculate ISD. The data were screened for extreme values (i.e., three SDs from the mean of each group), which were excluded from the analyses. This represents a conservative method of calculating IIV, as removing extreme values will likely reduce the extent of within-subject variability. Group-level mean values were imputed for any excluded trials, which represented 1.3%, 3.3%, and 3.8% of trials for the SRT, CRT, and SSRT, respectively.

2.3. MRI data

2.3.1. Acquisition

MRI data were acquired on the same day as CTIP and SDMT administration, using a 1.5 T General Electric MRI and standard eight channel head coil. DTI acquisition used a spin-echo echo planar imaging sequence. One image with no diffusion weighting was collected, followed by 55 diffusion-weighted images with the following parameters: TR = 12 s, TE = 71.2 ms, b-value = 850 s/mm², FOV = 260 mm², 128 × 128 matrix, and 45 3 mm axial slices. A T1-weighted anatomical image was also acquired, using a spoiled gradient recalled (SPGR) sequence (TR / TE = 25/5 ms, 40 degree flip angle, FOV = 240 mm², 256 × 256 matrix, and 124 1.5 mm axial slices). In addition, a T2-weighted fluid-attenuated inversion recovery (FLAIR) image was acquired (TR / TE / TI = 8000/120/2000 ms, two averages, FOV = 240 mm², 256 × 224 matrix, and 56 3 mm axial slices).

2.3.2. Analysis

2.3.2.1. Conventional MRI. The Lesion Segmentation Toolbox (LST) (Schmidt et al., 2012) was used to automatically identify T2 hyperintense lesions in the MS participants on the basis of a T1-weighted and FLAIR image. Before employing LST, we first registered the T1-weighted and FLAIR images and resampled both images to a common resolution (.47 × .47 × 1.5 mm³) using FMRIB Software Library's (FSL) FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Preliminary testing suggested that LST performed better when this pre-processing step was performed (based on visual inspection of the lesion segmentation results overlaid on the FLAIR images).

To evaluate lesion burden at the group level, the binary lesion masks output by LST were transformed to standard space using a two-step procedure. First, the FLAIR images were linearly registered to DTI space (using the image with no diffusion weighting as the target). This transformation was applied to the binary lesion mask. Second, the nonlinear warp to standard space, defined in the DTI analysis (see Section 2.3.2.2), was applied to these transformed binary lesion maps. The group lesion map was computed such that voxels in which greater than or equal to 30% of MS participants had lesions were included (threshold based on (Yu et al., 2012)).

Brain parenchymal fraction (BPF) (Phillips et al., 1998) was calculated from the partial volume estimate maps of the three tissue classes, segmented in Statistical Parametric Mapping 8 (SPM8) (The FIL Methods Group, 2013) and its Voxel-Based Morphometry Toolbox (VBM8) (Gaser, n.d.) after lesion filling in LST. Defined as the fraction of the combined volume of gray matter and white matter divided by the total intracranial volume, BPF is an established technique to investigate global brain atrophy (De Stefano et al., 2007).

The relations between behavioral measures and both lesions and BPF were evaluated, in the MS participant group only, using correlation analysis in SPSS (IBM Corporation, 2011). Age was included as a covariate of no interest.

2.3.2.2. DTI. DTI data were analyzed using FSL 5.0.2 (Smith et al., 2004). FSL's Diffusion Toolbox was used to correct for participant motion and image distortions due to eddy currents. The diffusion vector was also corrected for participant motion, based on the output of the eddy current correction. The diffusion tensor was fit to each voxel using DTIFIT. The data was then brain extracted using BET (Smith, 2002). The resulting FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) maps were input into tract-based spatial statistics (TBSS) (Smith et al., 2006; Smith et al., 2007). In TBSS, all subjects' FA data are aligned into a common space (registration target: FMRIB58_FA 1 mm) using the nonlinear registration tool FNIRT (Andersson et al., 2007a; Andersson et al., 2007b; Rueckert et al., 1999). For each patient, a binary exclusion mask representing voxels that were identified as lesions (see Section 2.3.2.1) was input to FNIRT to avoid excessive warping in lesioned brain areas. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to all participants. Each participant's aligned FA data were then projected onto this skeleton (thresholded at FA > .3). The MD, RD, and AD maps were transformed to standard space (using the warps defined based on the FA maps as described above), and projected onto the thresholded FA skeleton.

The resulting FA, MD, RD, and AD data were input into voxel-wise cross-subject statistics. We evaluated the statistical significance of between-group differences in FA, MD, RD, and AD, as well as correlations between these DTI metrics and behavioral performance on all three CTIP subtests, for both mean reaction time (RT) and ISD (calculated as described in Section 2.2.2.2). We also evaluated the relation between SDMT score and DTI metrics. To do so, voxel-wise permutation tests were performed (Nichols and Holmes, 2002), as implemented by FSL's randomise software (5000 permutations, *p* < .01, corrected for multiple comparisons using threshold-free cluster enhancement (Smith and Nichols, 2009)). Each behavioral measure was modeled separately, with one covariate for each group. Age was included in all TBSS analyses as a covariate of no interest. Regressors were mean-centered before being input to the analyses.

2.3.2.3. Regions of interest. Both TBSS and lesion data were considered with respect to 16 regions of interest (ROIs) from the JHU ICBM-DTI-81 white matter labels atlas in FSL (Mori et al., 2008) (see Appendix A). The lesion load of each region was calculated based on the percentage of voxels in the ROI that were classified as lesions in the group lesion map. To evaluate TBSS results with respect to each ROI, the number of FA skeleton voxels in each ROI was determined. An ROI was considered related to a particular measure if greater than or equal to 40% of its skeleton voxels showed a significant effect in the TBSS analysis (threshold based on (Yu et al., 2012)).

3. Results

3.1. Clinical measures

Demographic, clinical, and test result data for the MS and control participant groups are presented in Table 1. The MS participants'

median EDSS score was 2.25 (range: 1–3.5). MS participants did not report significantly higher levels of depression than controls and did not differ from controls on the basis of age or years of education.

3.2. Tests of information processing speed

The test results for the SDMT and CTIP subtests are summarized in Table 1. While MS participants obtained somewhat lower scores than controls on the SDMT, the group difference was not statistically significant ($t(38) = 1.73, p = .09$). Accuracy data is not recorded for the SRT. Both MS participants and controls performed the CRT and SSRT with 98% accuracy (mean \pm standard deviation; CRT: $M_{MS} = 29.45 \pm .83; M_{Controls} = 29.65 \pm .74$; SSRT: $M_{MS} = 29.45 \pm .83; M_{Controls} = 29.65 \pm .74$). MS participants had significantly longer mean RTs on both the SRT ($t(37.8) = 2.8; p < .01$) and SSRT ($t(38) = 3.2; p < .005$), but not on the CRT ($t(38) = 1.6; p = .12$).

As with the mean RT results, MS participants demonstrated larger ISDs (i.e., worse performance) on the SRT ($t(38) = 3.03; p < .005$) and the SSRT subtests ($t(38) = 2.8; p < .01$), though not on the CRT subtest ($t(38) = .9; p = .38$).

Correlations between pairs of behavioral measures were examined for the MS participant group only. SDMT scores were not significantly correlated with mean RT on the SRT subtest of the CTIP ($r = -.40; p = .09$) but were correlated with both CRT ($r = -.52; p < .05$) and SSRT ($r = -.57; p < .01$) mean RT. SDMT scores were also correlated with ISD for the SSRT subtest of the CTIP ($r = -.45; p < .05$), though not with ISD for the SRT ($r = -.31; p = .19$) or CRT ($r = -.21; p = .39$) subtests.

3.3. Atrophy and lesions

3.3.1. Group differences

Brain parenchyma fraction (BPF; mean \pm standard deviation) was significantly lower in MS patients ($81.8 \pm 2.9\%$) than controls ($84.4 \pm 2.1\%$; $t(38) = 3.24; p < .005$). The mean lesion load of the MS patients was 15.8 ± 24.5 ml, which was equivalent to $1.2 \pm 1.9\%$ of total intracranial volume, or $1.6 \pm 2.5\%$ of total parenchymal volume.

3.3.2. Relations to behavioral measures

The relations between behavioral measures, BPF, and lesion volume (fraction of total parenchymal volume) were examined for the MS patients only (Table 2). SDMT performance was not significantly correlated with BPF, but was correlated with lesion volume. BPF was correlated with mean performance on the SRT and SSRT subtests of the CTIP, while for ISD this correlation was significant only for the

Table 2

Correlation analysis between behavioral measures and BPF and lesion volume (fraction of total parenchymal volume) for the MS participant group.

Behavioral measure	BPF		Lesion load	
	R	p	R	p
^a SDMT	0.405	0.085	−0.533	0.019
^b CTIP-SRT Mean	−0.582	0.009	0.536	0.018
^b CTIP-CRT Mean	−0.156	0.524	0.458	0.048
^b CTIP-SSRT Mean	−0.528	0.020	0.596	0.007
^b CTIP-SRT ISD	−0.484	0.036	0.633	0.004
^b CTIP-CRT ISD	−0.161	0.510	0.222	0.362
^b CTIP-SSRT ISD	−0.314	0.190	0.487	0.019

^a Higher scores indicate better performance.
^b Higher scores indicate worse performance.

SRT subtest. Lesion volume was correlated with both mean performance and ISD on the SRT and SSRT subtests, as well as with mean performance on the CRT subtest.

The ROI analysis of group level lesion volumes is presented in Table 3. In this sample of MS participants, lesion load was most pronounced in the corona radiata and posterior thalamic radiation, with greater than 25% of voxels in these ROIs identified as lesions. Lesions were also observed in the sagittal stratum, superior frontal–occipital fasciculus, superior longitudinal fasciculus, the corpus callosum (body, genu, and splenium), and internal capsule ROIs.

3.4. DTI

3.4.1. Group differences

TBSS analysis revealed group differences in all DTI metrics across numerous regions of white matter, with lower FA and higher diffusivity (MD, RD, and AD) in MS participants compared to controls. No examples of the reverse (i.e., higher FA and/or lower diffusivity in MS participants) were observed in our sample. Suprathreshold effects (i.e., significant TBSS results in >40% of skeletal voxels in the ROI (Yu et al., 2012)) were observed in the sagittal stratum, the superior longitudinal fasciculus, the corpus callosum (body, genu, and splenium), the corona radiata, and the posterior thalamic radiation (Table 3). Fig. 1 displays significant group differences in FA as determined by TBSS analysis, overlaid on the group lesion map. Note that the TBSS analysis revealed greater percentages of affected tissue than the group level lesion volume analysis (Table 3), with microstructural differences between MS patients and controls extending beyond regions identified as lesions into areas of NAWM. The increased percentage of affected ROI for DTI metrics relative to lesion burden is highlighted in Fig. 2, which depicts the group differences in FA and group lesion map in the splenium of the corpus callosum – an example of an ROI with limited lesions but extensive FA differences between MS patients and controls.

3.4.2. Relations to behavioral measures

The ROI analysis of the correlations between behavioral measures and DTI metrics of the MS participants, as determined by TBSS, is summarized in Table 4. Each behavioral measure was modeled separately, with one covariate for each group. As described in Section 2.2.2.2, the ISD calculation uses regression to parcel out systematic factors that can affect variability, and ensures that differences in variability are not a statistical artifact of differences in individual or group mean performance (Hultsch et al., 2000). No suprathreshold relations were observed for the CRT or SSRT, for either mean-level performance or ISD (data not shown). For control participants, no voxels demonstrated significant relations between any DTI metric and any behavioral measure (data not shown).

For MS patients, numerous relations between DTI metrics and behavioral measures were observed. In all instances, worse performance on behavioral measures was associated with decreased FA or

Table 1

Demographic information, clinical measures, and information processing speed test results for the MS and control groups (mean \pm standard deviation except where indicated otherwise).

	MS participants	Control participants	p
N ^a	20	20	
Age (years)	42.4 \pm 6.3	42.5 \pm 7.8	n.s.
Education (years)	14.6 \pm 1.8	15.1 \pm 2.3	n.s.
EDSS ^b	2.25		n/a
Disease duration (years)	8.1 \pm 6.9		
BDI-Fast Screen	1.8 \pm 2.1	1.1 \pm 1.5	n.s.
SDMT (# of correct responses)	54.4 \pm 11.2	60.4 \pm 10.7	n.s.
SRT (msc)	410.4 \pm 63.8	351.5 \pm 68.5	<.01
CRT (ms)	664.2 \pm 121.4	592.4 \pm 163.0	n.s.
SSRT (ms)	1000.2 \pm 179.8	819.9 \pm 176.3	<.005
SRT (ISD)	8.2 \pm 3.0	5.7 \pm 2.0	<.005
CRT (ISD)	8.2 \pm 2.5	7.4 \pm 2.9	n.s.
SSRT (ISD)	9.3 \pm 2.2	7.6 \pm 1.9	<.01

^a Total.
^b Median.

Table 3
ROI analysis of group-level lesion findings and group differences on the DTI metrics evaluated using TBSS. For the TBSS analyses, bold font indicates ROIs that are suprathreshold (see Section 2.3.2 for details).

Tract	Lesions	FA (MS < C)	MD (MS > C)	RD (MS > C)	AD (MS > C)
	% of total ROI	% of skeletal ROI	% of skeletal ROI	% of skeletal ROI	% of skeletal ROI
Cingulum	0.0	14.9	12.1	24.6	1.7
External capsule	0.0	26.3	17.1	15.3	13.7
Fornix	0.0	0.0	0.0	0.0	0.0
Sagittal stratum	13.4	84.7	73.6	83.5	27.2
Superior frontal–occipital fasciculus	8.7	0.0	11.2	0.0	28.4
Superior longitudinal fasciculus	16.0	20.5	53.6	35.2	25.5
Uncinate fasciculus	0.0	0.0	2.2	0.0	1.5
Cerebral peduncle	0.0	9.5	0.0	0.0	0.4
Corticospinal tract	0.0	0.0	0.0	0.0	0.0
Medial lemniscus	0.0	0.0	0.0	0.0	0.0
Corpus callosum (body)	4.9	74.4	72.6	78.9	39.1
Corpus callosum (genu)	8.8	29.1	49.9	33.1	35.6
Corpus callosum (splenium)	3.4	72.8	88.0	82.8	61.8
Corona radiata	34.7	40.8	69.0	54.4	50.3
Internal capsule	1.4	15.6	29.5	16.5	31.8
Posterior thalamic radiation	27.4	83.4	75.4	88.0	33.8

MS: multiple sclerosis participant group.
C: control participant group.

increased MD, RD, or AD. SDMT performance was associated with DTI metrics for the body (FA) and genu (FA, MD, RD) of the corpus callosum, the posterior thalamic radiation (FA, MD, RD), and the superior longitudinal fasciculus (MD, RD). Mean CTIP SRT performance was associated with DTI metrics for the body (FA, MD, RD), genu (FA, MD, RD), and splenium (MD) of the corpus callosum, as well as for the posterior thalamic radiation (RD), the uncinate fasciculus (FA), and the corona radiata (RD). ISD on the SRT subtest of the CTIP was associated with DTI metrics in the greatest number of white matter fiber tracts. These again included the body (FA, MD, RD), genu (FA, MD, RD), and splenium (MD, AD) of the corpus callosum, as well as the posterior thalamic radiation (MD, RD), the uncinate fasciculus (FA), the corona radiata (MD, RD), and the superior longitudinal fasciculus (MD). In addition, associations of ISD were found for the external capsule (FA) and the superior frontal–occipital fasciculus (AD) that were not seen for either SDMT or mean CTIP SRT performance.

4. Discussion

Consistent with previous studies, we identified regions of reduced FA and increased diffusivity in the white matter of MS patients

relative to matched controls (Table 3; e.g., (Roosendaal et al., 2009; Kern et al., 2011; Yu et al., 2012; Onu et al., 2012; Bozzali et al., 2013)). The regions of reduced FA extended beyond lesions into NAWM (Figs. 1 and 2), confirming previous assertions regarding the greater sensitivity of DTI to MS-related white matter pathology relative to conventional MRI (e.g., (Roosendaal et al., 2009; Yu et al., 2012)). Despite the mild neurologic disability of our sample, we also observed reduced BPF in MS patients relative to controls, a finding also seen in previous studies of early stage or mildly affected relapsing–remitting MS patients (Chard et al., 2002; De Stefano et al., 2007).

SDMT performance was not significantly correlated with BPF (Table 2), a finding consistent with that of a previous study in which a broader range of clinical cognitive tests were examined (Sastre-Garriga et al., 2009). In contrast, we did observe a relation between SDMT performance and lesion burden (Table 2). Previous studies have produced mixed evidence with some studies having reported either no relation or a non-significant trend (Bomboi et al., 2011; Brochet et al., 2008), whereas other studies have reported a significant relation between lesion burden and SDMT performance for persons with MS (Rovaris et al., 2002; Stankiewicz et al., 2011).

TBSS analysis revealed that, for MS patients, white matter microstructural measures were correlated with SDMT performance in the

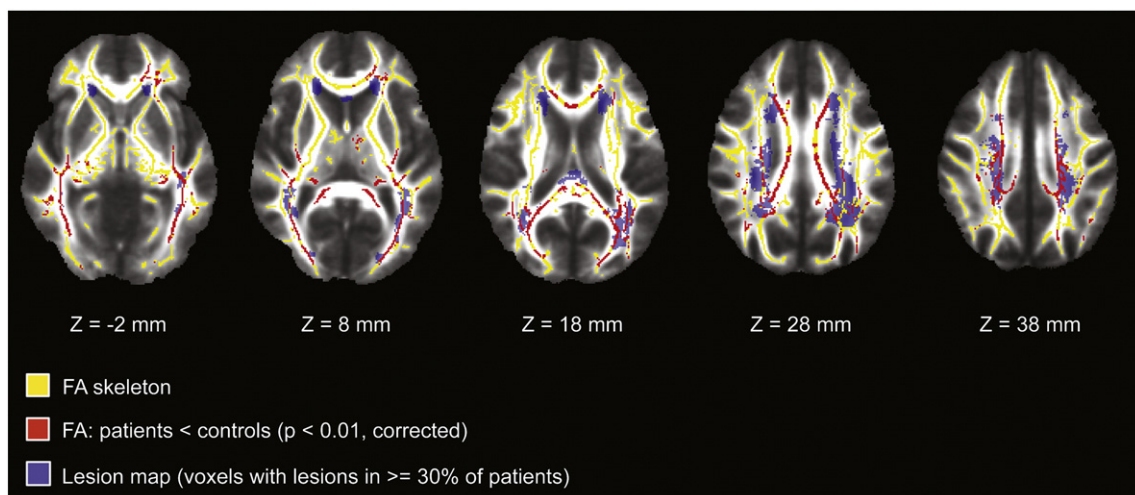


Fig. 1. Group lesion map and significant group differences (MS participants < controls) in FA based on the TBSS analysis. Results are overlaid on the mean FA image, in MNI space, with the z-positions of selected slices shown. Images are displayed using radiological convention.

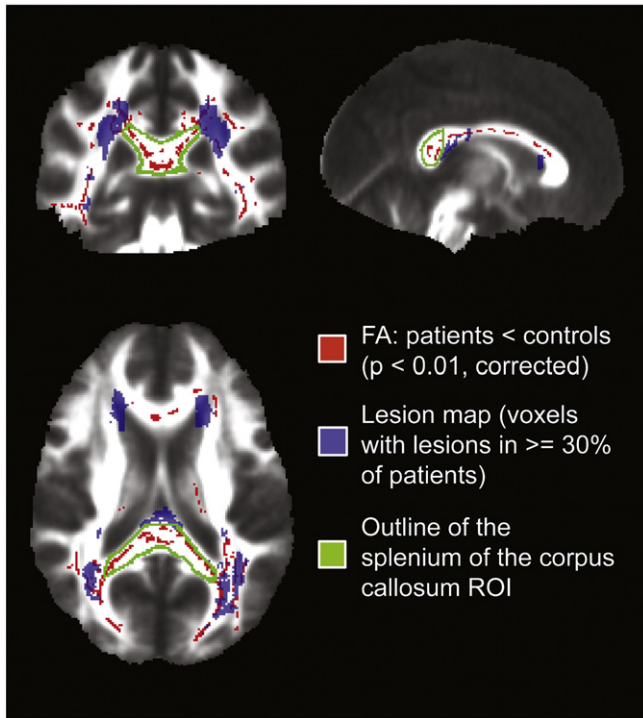


Fig. 2. Example of an ROI with minimal lesions, but widespread FA differences between MS participants and controls (splenium of the corpus callosum). Note that the TBSS analysis of FA was restricted to FA skeleton voxels (not shown; see Section 2.3.2.2 for details), whereas the group lesion map was not restricted. Top left: coronal section; top right: sagittal section; bottom left: axial section. Images are displayed using radiological convention.

superior longitudinal fasciculus, corpus callosum, and posterior thalamic radiation (Table 4). These findings were also observed by Yu et al. (2012), who further identified the external capsule, cingulum, sagittal stratum, fornix, uncinate fasciculus, corona radiata, internal capsule, and cerebral peduncle as related to SDMT performance. To our knowledge, no other studies have used a voxel-based approach to evaluate the relation between microstructure and SDMT performance in MS; however, previous studies have demonstrated correlations between SDMT performance and FA within an ROI of the midsagittal corpus callosum (de Medeiros Rimkus et al., 2011) and for the whole brain (Warlop et al., 2009). Thus, our findings add to

the limited available evidence suggesting that DTI metrics of white matter integrity are indeed sensitive to information processing speed, as measured by standard clinical tests, among mildly affected MS patients.

To our knowledge, ours is the first investigation of the relations between CTIP performance and structural brain imaging measures. Mean performance and IIV on CTIP subtests, particularly the SRT subtest, were related with both BPF and lesion load (Table 2). Furthermore, mean performance and IIV on the SRT subtest of the CTIP were significantly related to DTI measures (Table 4). Mean performance on the SRT subtest of the CTIP was significantly associated with DTI microstructural measures in the corpus callosum, the posterior thalamic radiation, the uncinate fasciculus and the corona radiata. While IIV on the SRT subtest was associated with DTI microstructural measures in these same regions, additional associations were found for the superior longitudinal fasciculus, the external capsule, and the superior frontal–occipital fasciculus.

In contrast to the SRT subtest, neither the CRT nor SSRT subtests had suprathreshold relations with DTI metrics, for either mean performance or IIV. Based on the current data, it is not clear why performance on the CRT or SSRT CTIP subtests was not also related to white matter microstructure. Differences in task demands might be an explanatory factor, as both the CRT and SSRT subtests require choosing between bimanual responses (i.e., participants must respond using one of two buttons) whereas the SRT requires only a unimanual response. Thus the CRT and SSRT subtests are more complex in their response requirements and are more cognitively demanding than the SRT subtest of the CTIP. While the SDMT could also be considered cognitively demanding, and conversely was associated with suprathreshold relations with DTI metrics, the SDMT has numerous other features that differ from the CTIP subtests, such as requiring a verbal rather than a manual response. It is possible that methods characterizing macrostructure and/or gray matter may be sensitive to neurologic correlates of CRT and SSRT performance that are not evident when using the TBSS approach employed in the current study. IIV on more cognitively demanding tasks might also be better characterized by examining functional connectivity (e.g., (Wojtowicz et al., 2012b)) and it seems likely that a comprehensive understanding of the neural correlates of IIV will require a multimodal imaging approach.

Speculations regarding the mechanisms of the link between IIV and white matter microstructure have been previously proposed based on data from healthy adults. In this context, it has been suggested that IIV reflects neural noise and disruptions of action potentials associated with decreased white matter integrity (Fjell et al.,

Table 4

Results of the TBSS analysis for the SDMT, CTIP-SRT mean, and CTIP-SRT ISD, for the MS participant group. In all cases, decreased FA and/or increased MD, RD, and AD was associated with worse performance. Bold font indicates ROIs for which suprathreshold relations were observed (see Section 2.3.2 for details).

Tract	% of skeletal voxels in ROI with significant effect in the TBSS analysis											
	SDMT				CTIP-SRT mean				CTIP-SRT ISD			
	FA	MD	RD	AD	FA	MD	RD	AD	FA	MD	RD	AD
Cingulum	15.2	3.2	8.2	0.0	16.6	4.2	9.6	0.0	14.6	9.8	17.4	0.5
External capsule	30.3	19.7	22.8	15.2	30.1	30.6	38.3	0.0	54.9	39.7	37.5	0.4
Fornix	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Sagittal stratum	27.5	21.9	33.0	0.0	16.5	26.1	30.6	0.0	32.0	30.9	36.9	0.0
Superior frontal–occipital fasciculus	0.0	0.0	0.0	0.0	0.0	19.0	0.9	0.0	0.0	25.9	19.0	42.2
Superior longitudinal fasciculus	37.4	40.4	41.4	0.0	1.9	10.0	19.5	0.0	1.7	40.6	24.4	31.0
Uncinate fasciculus	14.1	12.6	16.3	7.4	43.7	11.9	27.4	0.0	70.4	11.9	33.3	0.0
Cerebral peduncle	0.0	0.0	0.0	0.0	1.6	0.0	0.6	0.0	0.1	0.5	1.6	11.6
Corticospinal tract	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Medial lemniscus	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Corpus callosum (body)	40.5	16.9	37.1	0.0	55.7	41.3	57.7	0.0	47.9	49.7	60.0	28.4
Corpus callosum (genu)	79.6	42.7	71.6	0.0	65.1	50.8	61.5	0.0	70.3	67.7	73.9	31.7
Corpus callosum (splenium)	32.9	34.1	33.8	0.0	13.7	41.2	31.0	0.0	6.6	43.2	27.4	65.1
Corona radiata	27.1	18.5	26.0	0.3	33.2	33.6	46.9	0.3	37.1	54.7	54.5	31.0
Internal capsule	1.8	3.4	3.2	0.0	2.4	6.1	6.2	1.1	4.0	16.2	8.5	31.4
Posterior thalamic radiation	59.7	54.9	60.9	3.7	20.8	39.5	46.8	0.7	22.9	43.8	50.2	14.3

2011; MacDonald et al., 2009). Although the specific neurologic manifestations of response variability versus response slowing remain incompletely characterized, IIV may be the more sensitive indicator of white matter integrity as behavioral instabilities associated with neural noise become less evident when performance is averaged across trials.

To our knowledge, our study provides the first demonstration of a relation between intra-individual performance variability and DTI metrics in persons with MS. We demonstrated that, for our sample of mildly affected MS participants, increased IIV on the SRT subtest of the CTIP was associated with reduced integrity of multiple white matter regions, as measured by DTI. These results suggest that IIV may be a sensitive behavioral marker for neurologic dysfunction; consistent with findings of increased IIV in other neurologic disorders (reviewed in MacDonald et al. (2006) and MacDonald et al. (2009)). Our results imply that greater IIV is associated with reduced structural connectivity due to disease-related reductions in white matter integrity.

Increased IIV was associated with reduced white matter integrity in more tracts than either SDMT performance or mean performance on the SRT subtest of the CTIP. These findings provide preliminary evidence that IIV may be sensitive to a broader range of MS-related differences in tissue microstructure than are more commonly used tests of information processing speed. This link between IIV and white matter microstructure provides a possible neurologic basis for the findings of prior behavioral studies which reported that IIV was better able to discriminate MS patients from healthy controls than mean-level performance on timed tests (Bodling et al., 2012; Wojtowicz et al., 2012a; Wojtowicz et al., 2013). However, more research is needed into the neurologic correlates of IIV using larger and more representative samples of MS patients. In particular, examining the reproducibility of the current results with respect to the particular tracts implicated for each behavioral measure would provide valuable insight into understanding how the different white matter regions contribute to the overall neurologic and cognitive status of the patient.

More generally, our finding that IIV was sensitive to microstructural measures in more regions than mean-level performance highlights the potential that IIV holds for improving our understanding of the brain–behavior relationship. This sentiment is in line with recent studies of healthy individuals in which white matter integrity was linked to IIV in reaction time more so than mean reaction time on a flanker task (Fjell et al., 2011; Tamnes et al., 2012). Indeed, focusing on mean-level performance may be an oversimplification, particularly when studying persons with high IIV, such as neurological populations (MacDonald et al., 2009). Thus, there is mounting evidence that evaluating the distribution of behavioral responses (as opposed to evaluating mean-level performance only) will allow the neural basis of behavior to be better characterized.

Our study is subject to a number of limitations, including restrictions in our subject recruitment to mildly affected MS participants. Also, the CTIP includes only 30 trials per subtest and while previous studies of IIV have used similar numbers of test trials (e.g., (Burton et al., 2006; Dixon et al., 2007)) estimates of IIV might be improved by including more trials. We also considered only one measure of central tendency (mean) and one measure of variability (ISD) in this study. Although we have previously found that ISD better discriminated MS patients from controls than did coefficient of variation (Wojtowicz et al., 2012a), evaluating other measures of central tendency (e.g., median) as well as variability will be important for verifying the relative importance of IIV as a measure of cognitive dysfunction in MS.

The data analysis approach that we adopted in the current study modeled the behavioral measures as separate covariates for the two groups. We did not observe significant relations between DTI metrics and behavioral measures in the control group, suggesting that the

effects we observed are related to MS. However, studies of larger samples of healthy controls with a broader age range might reveal relations between DTI metrics and CTIP performance (e.g., (Fjell et al., 2011)). We also opted to analyze mean performance and IIV (corrected for individual mean performance) in separate models. This approach provides greater sensitivity and was important for this initial investigation, although it limits our ability to determine the relative importance of the two variables. Multiple DTI metrics were evaluated in this study (FA, MD, RD, and AD) and while there is evidence from animal models that different DTI metrics have distinct physiological bases (e.g., radial diffusivity reflects myelin content (Song et al., 2002)), there remain outstanding issues to be resolved before these concepts can be applied to human studies (Wheeler-Kingshott and Cercignani, 2009). The goal of including multiple DTI metrics in our analyses was not to evaluate which physiological parameters relate to cognition, but rather to improve our sensitivity by capitalizing on the additional (albeit non-unique) information provided by each metric. Thus, we did not attempt to speculate on the specific physiological underpinnings of the DTI metrics used.

5. Conclusions

We demonstrated that mean performance and IIV on the CTIP are sensitive to neurologic manifestations of MS, including lesion burden, BPF, and DTI indices of white matter microstructure, even among mildly affected persons. In particular, our report highlights the potential value of considering metrics of within-person fluctuations in performance speed, in addition to mean-level performance, for exploring relationships between behavior and white matter integrity.

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Appendix A

Total volume and FA skeleton volume for the 16 ROIs investigated.

Tract	Category	ROI volume (ml)	
		Total	FA skeleton
Cingulum	Association fibers	7484	1293
External capsule	Association fibers	11,198	2557
Fornix	Association fibers	659	103
Sagittal stratum	Association fibers	4459	1036
Superior frontal–occipital fasciculus	Association fibers	1014	116
Superior longitudinal fasciculus	Association fibers	13,212	2838
Uncinate fasciculus	Association fibers	756	135
Cerebral peduncle	Brainstem tract	4556	1278
Corticospinal tract	Brainstem tract	2732	619
Medial lemniscus	Brainstem tract	1389	96
Corpus callosum (body)	Commissural fibers	13,711	3263
Corpus callosum (genu)	Commissural fibers	8851	1755
Corpus callosum (splenium)	Commissural fibers	12,729	2590
Corona radiata	Projection fibers	36,151	7646
Internal capsule	Projection fibers	18,646	4827
Posterior thalamic radiation	Projection fibers	7950	2154

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