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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.

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