

Response Variability Is Associated With Self-Reported Cognitive Fatigue in Multiple Sclerosis

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Cognitive fatigue is a common, often debilitating symptom of multiple sclerosis (MS). Although MS patients frequently report that fatigue negatively affects cognitive functioning, most studies have found little evidence for a direct relationship between self-reported cognitive fatigue and traditional measures of neuropsychological functioning. The purpose of the present study was to examine the association between self-reported cognitive fatigue and a measure of response time variability (RTV). MS patients demonstrated significantly higher RTV than controls, and RTV was highly correlated with self-reported cognitive fatigue among relapsing-remitting and secondary progressive MS patients. Results highlight the need to implement newer methods to further elucidate the relationship between cognitive fatigue and neuropsychological functioning in MS.

Keywords: fatigue, response time, response time variability, multiple sclerosis, effort

Fatigue is often considered to be one of the most debilitating symptoms of multiple sclerosis (MS; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). Between 53% and 87% of MS patients report significant fatigue (Strober & Arnett, 2005). Fatigue in MS is defined as an overwhelming sense of weariness or lack of energy, and is related to increased emotional difficulties, poorer quality of life, and difficulty maintaining employment (Barak & Achiron, 2006; Freal, Kraft, & Coryell, 1984; Jongbloed, 1998; Ritvo, Fisk, Archibald, Murray, & Field, 1996; Schwartz, Coulthard-Morris, & Zeng, 1996). The cause of fatigue in MS is likely multifactorial and has been associated with many variables, including microscopic white matter damage, frontal systems dysfunction, depression, sleep disturbance, and disability status (Bakshi, 2003; Strober & Arnett, 2005; Tartaglia et al., 2004; van Duinen, Renken, Maurits, & Zijdwind, 2007).

Despite the widespread nature and devastating consequences of fatigue in MS, few studies have consistently demonstrated a relationship between self-reported fatigue and objective behavioral measures designed to assess fatigue. The behavioral measurement of *cognitive* fatigue has been particularly difficult to evaluate. Cognitive fatigue is common in MS and is characterized by increased mental effort and limited mental endurance (Barak & Achiron, 2006). Although many patients report that cognitive fatigue contributes to their cognitive difficulties (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Krupp & Elkins, 2000; Schwartz et al., 1996), few studies have found a direct relationship between neuropsychological performance and self-reported cognitive fa-

tigue. The primary purpose of the present study was to examine the relationship between self-reported cognitive fatigue and an objective measure of response time consistency.

The most commonly employed means of objectively examining cognitive fatigue in MS has involved the repeated administration of various tests (see DeLuca, 2005). First, patients are given a battery of neuropsychological tests. These tests are followed by an intervening period during which patients participate in various cognitively demanding tasks. Finally, the battery of neuropsychological tasks is repeated. Poorer neuropsychological performance following the intervening period of mental exertion is presumed to be due to cognitive fatigue. However, studies employing variations of this methodology have had decidedly conflicting results. Whereas a few studies have found evidence for decrements in performance after sustained mental effort in MS (Krupp & Elkins, 2000; Kujala, Portin, Revonsuo, & Ruutiainen, 1995; Schwid et al., 2003), most have not (Caruso, LaRocca, & Foley, 1991; Jennekens-Schinkel, Sanders, Lanser, & Van der Velde, 1988; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Parmenter, Denney, & Lynch, 2003; Paul, Beatty, Schneider, Blanco, & Hames, 1998). Moreover, the relationship between self-reported cognitive fatigue and performance-based measures of fatigue has been tenuous and difficult to characterize.

A proposed alternative way to measure fatigue is to record response time variability (RTV) during a sustained mental task. People with low RTV perform repetitive cognitive tasks in a consistent manner; in contrast, people with high RTV are unable to maintain consistent response latencies. Various lines of evidence suggest that higher RTV is associated with cognitive fatigue. For instance, high RTV indicates vulnerability to the fatiguing effects of sleep deprivation (Lim, Choo, & Chee, 2007; M. E. Smith, McEvoy, & Gevins, 2002). High RTV is also associated with primary fatiguing disorders. Despite generally intact cognitive abilities, patients with chronic fatigue syndrome show greater intraindividual variability in cognitive performance than normal controls (Fuentes, Hunter, Strauss, & Hultsch, 2001; Scheffers,

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Johnson, Grafman, Dale, & Straus, 1992). In addition, increased RTV has been documented among various fatiguing neuropsychiatric conditions, including mild cognitive impairment, traumatic brain injury, and schizophrenia (Kaiser et al., 2007; Stuss, Murphy, Binns, & Alexander, 2003). It has been hypothesized that RTV may be a cognitive marker for poor top-down attentional and executive control mechanisms (Bellgrove, Hester, & Garavan, 2004). According to this theory, patients with larger RTV may have to exert more effort to consistently focus their attention and stay on task. Functional and structural neuroimaging studies support this theory and indicate that RTV is associated with frontal systems dysfunction, decreased white matter volume, and disruptions of thalamic and inferior parietal circuits (Bellgrove et al., 2004; Stuss et al., 2003; Walhovd & Fjell, 2007).

Similar brain systems are thought to be involved when MS patients experience fatigue. Research indicates that despite no significant change in reaction time performance, fatigued MS patients have increased activity in orbitofrontal areas during reaction time tasks (van Duinen et al., 2007). Fatigued MS patients also show reduced glucose metabolism in the bilateral prefrontal cortex and basal ganglia (Roelcke et al., 1997). In addition, self-reported fatigue in MS has been associated with diffuse axonal damage and hypoactivation of thalamus, rolandic operculum, and intraparietal sulcus (Filippi et al., 2002; Tartaglia et al., 2004). These findings lend partial support to the hypothesis that striatal–thalamic–frontal systems play an important role in the formation of fatigue in MS (Chaudhuri & Behan, 2000). Taken together, functional imaging studies suggest that both self-reported fatigue in MS and RTV in various populations are primarily associated with white matter damage and frontal systems dysfunction.

Despite the implication of dysfunction associated with similar brain regions, evidence for increased RTV in fatiguing disorders, and a strong relationship between RTV and sleep deprivation, to date no study has examined the association between RTV and self-reported fatigue in MS. The purpose of the present study was twofold. First, we examined the difference between MS patients and controls on a simple test of effort that measures RTV. We hypothesized that MS patients would show increased RTV when compared with normal controls. Second, we hypothesized that more self-reported cognitive fatigue would be associated with higher RTV. Finally, we intended to conduct follow-up exploratory analyses examining the association among RTV, neuropsychological measures, and self-reported physical and social fatigue.

Method

Participants and Procedure

Patients were recruited from an advertisement placed in a newsletter distributed to individuals with MS in western Pennsylvania, MS support groups in central Pennsylvania, and fliers distributed in the State College, Pennsylvania, community. MS diagnoses were confirmed by a board-certified neurologist who also assessed disease course on the basis of Lublin and Reingold (1996) criteria. All but two patients met McDonald et al. (2001) criteria for MS, with these two patients having possible MS. None of the patients included in the current study had experienced a clinical exacerbation within 1 month prior to the evaluation. Participants were not included in the study if they had a history of (a) neurological disease other than MS, (b) drug or alcohol abuse, (c) learning

disability, or (d) motor impairments that would significantly alter test administration procedures. In addition, participants were excluded if they reported visual problems that prevented them from reading standard newsprint. In addition, participants were excluded if they scored below established cutoffs (<90% accuracy) on the Computerized Assessment of Response Bias (CARB). This was done to ensure that all of the participants in this study were motivated to perform well during the evaluation. After establishing informed consent, graduate students trained by a clinical neuropsychologist (P.A.) administered a variety of measures assessing physical, cognitive, and emotional functioning. In return for their participation, MS patients were given \$100 and a brief neuropsychological report. Normal controls were recruited by asking MS patients to recruit interested friends and by distributing fliers in central Pennsylvania. Controls were included if they had no major neurological or physical illnesses that would affect their testing. They were also given \$100 for their participation and a brief neuropsychological report on request. The study was approved by the Institutional Review Board at Pennsylvania State University.

Measures

Neuropsychological measures.

CARB (Allen, Conder, Green, & Cox, 1997). The CARB was used to measure response time and response variability. Participants were asked to remember a series of digits on a computer screen. Next, the screen went blank and a distraction task was initiated (backward counting). Finally, participants were shown two series of digits and pressed one of the two *Shift* keys on a keyboard to indicate which series they were asked to remember. In total, participants responded to 111 forced-choice events. The task was split into three blocks of 37 events each. Participants endured a slightly longer distraction period after each successive block. Despite primarily being known as a measure of response validity, the CARB incorporates the fundamental characteristics of most standard RTV measures. For instance, like most RTV measures, the CARB employs a simple forced-choice paradigm that records precise reaction time data, presents multiple trials, requires sustained attention, and emphasizes simple decision making. Variables of interest for the current study included mean correct response time for each block, total response time, RTV for each block, and total RTV. RTV was calculated as the standard deviation of the correct response times.

Shipley Institute of Living Scale (Zachary, 1986). The Vocabulary subscale of the Shipley Institute of Living Scale was used to estimate current intellectual functioning.

Symbol Digit Modalities Test (SDMT; A. Smith, 1982). The oral version of the SDMT was used as a measure of attention and information processing speed. During this task, participants used a key to match symbols with numbers. The dependent variable was the total number of correct responses in 90 s.

The Visual Elevator subtest from the Test of Everyday Attention (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). The Visual Elevator task was designed to be an ecologically valid measure of information processing speed and mental flexibility. Examinees were shown a series of elevators on a stimulus sheet. Interspersed among the elevators, an occasional arrow pointed up or down to indicate the direction the elevator was traveling. Par-

Participants were asked to quickly count the elevators to indicate which floor they were on; when they encountered a *down* arrow they reverse counted and when they encountered an *up* arrow they counted forward consecutively. There were a total of 40 switches of direction across 10 trials. The variable of interest for the present study was the average time per correct switch.

Selective Reminding Test (SRT; Strauss, Sherman, & Spreen, 2006). The Long-Term Storage (LTS) and Consistent Long-Term Retrieval (CLTR) indices from the SRT were used as measures of learning and memory. During this task, the examiner read a list of 12 words and the participant was asked to recall as many words as possible. Words that the participant was unable to recall were repeated over five additional trials.

Self-Report measures.

Fatigue Impact Scale (FIS; Fisk et al., 1994). The FIS is a 40-item self-report measure of fatigue that is commonly used in MS. It comprises three subscales measuring physical (“Because of my fatigue, I have trouble maintaining physical effort for long periods”), social (“Because of my fatigue, I am less motivated to engage in social activities”), and cognitive (“Because of my fatigue, I feel less alert”) fatigue. Participants were asked to rate how much of a problem fatigue has caused them in the past month on a 0 (*no problem*) to 4 (*extreme problem*) Likert scale. The FIS has good reliability and has been shown to differentiate patients with fatiguing and nonfatiguing medical disorders (Fisk et al., 1994; Kos et al., 2005).

Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995). Because more traditional measures may overestimate depression in neurological samples, the 14-item Mood and Evaluative subscales of the CMDI were used to assess depressive symptomatology in this study. The CMDI has been shown to be a reliable and valid self-report measure of depression in MS.

Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS is a measure of MS disease progression and neurological impairment. It is commonly used in both clinical practice and MS research. Participants were asked to rate their functional abilities in a number of different physical domains. Self-report EDSS scales have been found to be highly correlated with neurologists’ independent ratings (Solari et al., 1993).

Results

Preliminary Analyses

Six MS patients were not included in the study. One had a history of electroconvulsive therapy; 1 reported a history of stroke after testing was completed; and 4 scored below an established cutoff (<90% accuracy) on the CARB. Eighty-seven MS patients (70 relapsing-remitting and 17 secondary progressive) and 24 controls were included in the study. Seventy-two of the MS patients and 20 of the controls were women. The mean ± SD age for MS patients was 47.05 ± 9.05 years, with 14.25 ± 2.00 years of education and an estimated IQ of 104.93 ± 9.15. The mean ± SD diagnosis duration was 10.86 ± 7.98 years, and the mean ± SD EDSS score was 4.50 ± 1.57. No MS patients were taking disease-modifying steroids at the time of the evaluation (e.g., methylprednisone). Results of *t* tests revealed no significant relationships between self-reported cognitive fatigue and the use of selective serotonin reuptake inhibitors, benzodiazepines, narcotics, muscle relaxants, antiepileptics, or psychostimulants (*ps* > .1).

The mean ± SD age for the control group was 47.38 ± 12.00 years, with 15.08 ± 2.24 years of education and an estimated IQ of 106.54 ± 10.89. Results of *t* tests revealed no significant differences between MS and control groups on measures of age, education, or estimated intelligence. Chi-square tests revealed no significant difference between the groups’ gender compositions. Kolmogorov–Smirnov testing revealed that reaction times and RTV were not normally distributed (*p* < .05); natural log transformations corrected for these violations.

Analyses between MS patients and controls. Descriptive information outlining group differences in self-reported fatigue, RTV, and response time is shown in Table 1. As expected, MS patients reported significantly more cognitive, physical, and social fatigue than controls. They also demonstrated longer response times and increased RTV. MS patients (49.78 ± 10.18) performed worse on the SDMT than controls (59.48 ± 8.55), *t*(108) = -4.19, *p* < .001, Cohen’s *d* = 1.03. A nonsignificant trend was observed suggesting MS patients (4.10 ± 1.18) also performed more poorly than controls (3.59 ± .73) on the Visual Elevator, *t*(106) = 1.94,

Table 1
Differences Between MS Patients and Controls on Measures of Self-Reported Fatigue, Response Time, and Response Time Variability

Variable	MS		Control		ln MS		ln Control		Cohen’s <i>d</i>	<i>t</i> (<i>df</i>)	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Total fatigue	62.9	28.6	16.4	17.9	—	—	—	—	1.95	9.75(59)	<.001
Cognitive fatigue	15.2	9.1	4.8	4.0	—	—	—	—	1.48	8.22(88)	<.001
Physical fatigue	19.6	9.7	4.8	7.3	—	—	—	—	1.72	8.32(50)	<.001
Social fatigue	28.1	14.2	6.8	9.7	—	—	—	—	1.75	8.53(53)	<.001
Total RTV	421	262	290	118	5.91	0.50	5.60	0.37	0.71	2.79(109)	<.01
RTV Block 1	405	294	312	176	5.86	0.50	5.62	0.49	0.48	2.06(109)	<.05
RTV Block 2	383	276	235	109	5.75	0.60	5.38	0.41	0.72	2.89(109)	<.01
RTV Block 3	395	274	262	116	5.82	0.54	5.49	0.40	0.69	2.78(109)	<.01
Total RT	1260	486	958	198	7.08	0.32	6.84	0.22	0.87	2.33(109)	<.01
RT Block 1	1294	495	1028	249	7.11	0.32	6.91	0.25	0.70	2.84(109)	<.01
RT Block 2	1229	522	920	192	7.04	0.41	6.80	0.22	0.73	2.66(109)	<.01
RT Block 3	1247	500	926	188	7.07	0.34	6.81	0.21	0.92	3.50(109)	<.01

Note. MS = Multiple Sclerosis; RTV = Response Time Variability in milliseconds, the standard deviation of correct response times; RT = Response Time in milliseconds; ln = natural log values. For *t* tests, RTV and RT were natural log transformed to correct for skewness. Fatigue was measured using the total score and Cognitive, Physical, and Social Fatigue subscales from the Fatigue Impact Scale.

$p < .1$, Cohen's $d = 0.52$. No differences were observed between MS patients and controls on measures assessing depression (mean CMDI t -score = 50.89 ± 11.18 vs. 47.45 ± 8.39 , respectively) or learning and memory.

RTV and cognitive fatigue in MS patients. Table 2 shows the Pearson product-moment correlations between self-reported measures and neuropsychological performance. Self-reported cognitive fatigue was significantly correlated with total RTV ($r = .45$, $p < .001$) and total response time ($r = .33$, $p < .01$). Cognitive fatigue was also positively associated with RTV and response time performance on all three performance blocks: Blocks 1 ($r = .50$, $p < .001$, and $r = .35$, $p < .01$, respectively), 2 ($r = .32$, $p < .01$, and $r = .25$, $p < .05$), and 3 ($r = .43$, $p < .001$, and $r = .32$, $p < .01$). As all of the RTV and response time variables were significantly correlated with self-reported cognitive fatigue, total RTV and total response time were employed in subsequent analyses. Partial correlation controlling for response time revealed a significant relationship between total RTV and cognitive fatigue ($r = .32$, $p < .01$). In contrast, no significant relationship was found between total response time and cognitive fatigue when controlling for total RTV. Partial correlation controlling for SDMT also revealed a significant relationship between total RTV and cognitive fatigue ($r = .38$, $p < .001$). SDMT was not significantly correlated with cognitive fatigue when controlling for total RTV ($r = -.07$, ns). Demographic (e.g., age, education, gender) and clinical variables were not associated with self-reported cognitive fatigue. Stepwise regression (entrance criteria $p = .05$ and exit criteria $p = .1$) revealed that only total RTV accounted for unique variance in self-reported cognitive fatigue.

RTV, social fatigue, and physical fatigue in MS patients. Self-reported physical fatigue was significantly correlated with total RTV ($r = .28$, $p = .01$) and total response time ($r = .28$, $p < .01$). Physical fatigue was also significantly correlated with EDSS ($r = .63$, $p < .001$), diagnosis duration ($r = .32$, $p < .01$), CMDI ($r = .26$, $p < .05$), SDMT ($r = -.32$, $p < .01$), age ($r = .21$, $p < .05$), LTS from the SRT ($r = -.23$, $p < .05$), and CLTR from the SRT ($r = -.23$, $p < .05$). Variables significantly associated with physical fatigue were entered into a stepwise regression. Only

EDSS, $\Delta R^2 = .40$, $\Delta F = 56.01$, $p < .001$, and total RTV, $\Delta R^2 = .03$, $\Delta F = 4.06$, $p < .05$, accounted for unique variance in physical fatigue.

Self-reported social fatigue was significantly correlated with total RTV ($r = .35$, $p < .01$) and total response time ($r = .32$, $p < .01$). Social fatigue was also significantly correlated with EDSS ($r = .54$, $p < .001$), diagnosis duration ($r = .33$, $p < .01$), CMDI ($r = .42$, $p < .001$), SDMT ($r = -.32$, $p < .01$), and VE ($r = .28$, $p < .01$). Variables significantly associated with social fatigue were entered into a stepwise regression. EDSS, $\Delta R^2 = .30$, $\Delta F = 35.03$, $p < .001$, CMDI, $\Delta R^2 = .09$, $\Delta F = 11.55$, $p < .01$, and total RTV, $\Delta R^2 = .05$, $\Delta F = 7.25$, $p < .01$, accounted for unique variance in social fatigue.

Follow-up Analyses

Exploratory analyses were conducted to determine whether the relationship between RTV and fatigue remained significant after separating MS subtypes. Secondary progressive patients reported more physical (secondary progressive patients $M = 27.12 \pm 6.51$; relapsing-remitting patients $M = 17.73 \pm 9.44$) and social fatigue (secondary progressive patients $M = 37.24 \pm 11.29$; relapsing-remitting patients $M = 25.90 \pm 13.95$) than relapsing-remitting patients, $t(85) = 3.87$, $p < .001$, Cohen's $d = 1.16$, and $t(85) = 3.11$, $p < .01$, Cohen's $d = 0.89$, respectively. Secondary progressive (15.89 ± 8.68) and relapsing-remitting (15.04 ± 9.24) patients did not differ significantly on the Cognitive Fatigue subscale. Secondary progressive ($7.22 \pm .41$) patients had significantly slower response times than patients with relapsing-remitting MS ($7.05 \pm .29$), $t(85) = 2.03$, $p < .05$, Cohen's $d = 0.48$. No significant difference was observed between secondary progressive ($5.94 \pm .63$) and relapsing-remitting ($5.90 \pm .47$) patients on total RTV.

Among relapsing-remitting MS patients, total RTV was significantly associated with cognitive ($r = .40$, $p < .01$), social ($r = .44$, $p < .001$), and physical ($r = .41$, $p < .001$) fatigue. Because total RTV and fatigue subtypes demonstrated similar effects among relapsing-remitting patients, the association between total

Table 2
Correlations Between Self-Reported Fatigue and Variables of Interest

Item	Cognitive fatigue	Physical fatigue	Social fatigue	Total RTV	Total RT	EDSS	Duration	CMDI	SDMT	VE	SRT LTS	SRT CLTR
Cognitive fatigue	1.00	.33**	.64**	.45***	.33**	.14	.12	.14	-.26*	.19	.01	-.03
Physical fatigue		1.00	.79***	.28**	.28**	.63***	.32**	.26*	-.32**	.19	-.23*	-.23*
Social fatigue			1.00	.35**	.32**	.54***	.33**	.42***	-.32**	.28**	-.14	-.18
Total RTV				1.00	.74***	.18	.23*	.05	-.46**	.42**	-.14	-.10
Total RT					1.00	.24*	.27*	-.03	-.51***	.31**	-.10	-.03
EDSS						1.00	.38***	.24*	-.45***	.28**	-.21	-.15
Duration							1.00	.17	-.34**	.17	-.24*	-.15
CMDI								1.00	-.03	.1	-.03	-.02
SDMT									1.00	-.47***	.38***	.35**
VE										1.00	-.21	-.25*
SRT LTS											1.00	.83***
SRT CLTR												1.00

Note. Total fatigue and subscales measured by the Fatigue Impact Scale; RTV = Response Time Variability; RT = Response Time; EDSS = Expanded Disability Status Scale; Duration = Duration of diagnosis in years; CMDI = Chicago Multiscale Depression Inventory; SDMT = Symbol Digit Modalities Test; VE = Visual Elevator; SRT = Selective Reminding Test; LTS = Long-Term Storage; CLTR = Consistent Long-Term Retrieval.

* $p < .05$. ** $p < .01$. *** $p < .001$.

RTV and total fatigue was explored. As would be expected, the correlation between total RTV and total fatigue on the FIS was highly significant ($r = .48, p < .001$; see Figure 1). Diagnostic statistics revealed one outlier (Cook's $D = .16$); when this outlier was removed, the association between total fatigue and total RTV increased ($r = .53, p < .001$). Total response time was also related to cognitive ($r = .32, p < .01$), social ($r = .39, p < .001$), physical ($r = .34, p < .01$), and total fatigue ($r = .38, p = .001$) in relapsing-remitting patients. Partial correlation controlling for total response time revealed a significant relationship between total RTV and total fatigue ($r = .30, p < .05$). Total fatigue and total reaction time were not related when controlling for total RTV ($r = .12, ns$).

Among secondary progressive MS patients, total RTV was associated with cognitive fatigue ($r = .63, p < .01$) but not social ($r = .10, ns$) or physical ($r = -.25, ns$) fatigue. No significant relationship was found between total response time and any measure of fatigue among patients with secondary progressive MS.

Among controls, total RTV was significantly associated with self-reported cognitive fatigue ($r = .48, p < .05$) but not social ($r = .31, ns$) or physical ($r = .26, ns$) fatigue. No significant relationship was found between total mean response time and fatigue among controls.

Discussion

Response time variability measures aspects of executive functioning related to a person's ability to consistently focus and purposefully sustain mental effort. Caused primarily by frontal systems dysfunction and white matter damage, increased RTV is associated with various fatiguing conditions and fatigue due to sleep deprivation. This was the first study to examine RTV among patients with MS. Consistent with hypotheses and results found in other neurological populations, MS patients exhibited increased RTV and response latency when compared with controls. Synchronously, RTV was significantly associated with self-reported cog-

nitive fatigue. RTV was the strongest predictor of self-reported cognitive fatigue, accounting for as much as 25% of the variance in the combined MS sample, 23% of the variance among controls, and 40% of the variance among patients with secondary progressive MS. Of note, measures of information processing speed (response time and SDMT) were also moderately correlated with cognitive fatigue in this study. However, partial correlations revealed that information processing speed measures were not correlated with cognitive fatigue when controlling for RTV. In contrast, RTV remained significantly correlated with cognitive fatigue even after controlling for measures of information processing speed. These findings suggest that RTV may act as a mediator between information processing speed and self-reported cognitive fatigue.

The present methodology offers advantages when compared with more traditional approaches that attempt to objectively measure cognitive fatigue. Traditionally, MS patients undergo a repeated series of neuropsychological tests. A decrement in performance over time is presumed to be due to cognitive fatigue. This approach is intuitive. However, it is very time consuming and results have been mixed. This methodology also rests on the assumption that fatigue is longitudinal and cumulative; that is, the longer one performs a task, the more cognitive fatigue he or she will experience. This accumulated fatigue is then supposed to account for an inferior repeat performance on neuropsychological tasks.

Results from this study suggest a different methodology may be worth exploring. Cognitive fatigue may not cause a linear decrement in neuropsychological performance with sustained mental effort, as has been assumed. Instead, fatigue may affect cognition by increasing response variability during individual mental tasks. In this manner, people who experience cognitive fatigue may have occasional lapses in attention; during these lapses, additional effort may be required to muster the necessary mental reserves to efficiently and consistently perform a designated task. Future studies should conduct multiple tests of performance variability to more fully ascertain the cognitive and neurologic mechanisms associated with the perception of cognitive fatigue. Moreover, a combination of traditional and newer methodologies may be fruitful. Although most studies find no significant decrement in repeat neuropsychological functioning following prolonged mental effort, there may be an increase in response variability as the duration of testing extends.

Albeit to a lesser extent, RTV was also associated with physical and social fatigue. RTV was significantly related to scores on the Physical and Social Fatigue subscales in relapsing-remitting patients, but was unrelated to scores on those subscales among secondary progressive patients and controls. Among the entire MS sample, disability status and RTV were the only variables to account for unique variance in self-reported physical fatigue. Disability status, self-reported depression, and RTV accounted for unique variance in self-reported social fatigue. These findings reinforce the notion that, even though RTV is a strong predictor of self-reported cognitive fatigue, RTV may not solely be an indicator of difficulty sustaining *cognitive* effort. It may be that increased RTV is partially induced by the physical fatigue of pushing a response key or the social fatigue of being in an unfamiliar

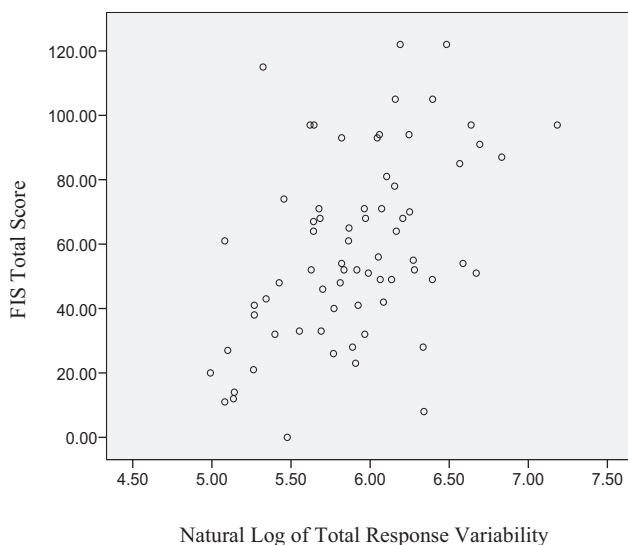


Figure 1. Association between Fatigue Impact Scale (FIS) and total response variability among relapsing-remitting multiple sclerosis patients.

environment. Consequently, future studies may want to study the relationship among RTV and physical, social, and other domains of functioning.

Given the correlational nature of the study, definitive causative statements cannot be entertained. It is equally plausible that increased RTV results in the perception of fatigue, that fatigue causes increased RTV, or that a third variable (e.g., white matter integrity, frontal systems dysfunction) results in both increased RTV and increased fatigue. An additional limitation of this study is the use of only one nontraditional measure of RTV. Because the CARB is traditionally considered a test of effort and motivation, it could also be argued that the observed relationship between fatigue and RTV is a consequence of fluctuations in motivation. Although the need to increase effort is inextricably linked to the perception of fatigue, we would argue that it is highly unlikely that the fatigued patients in this study lacked motivation. Indeed, none of the participants had readily identifiable reasons for malingering, no one in this study scored below established cutoffs indicating substandard motivation, and only the response times for correct responses were included in analyses. Nevertheless, future studies may wish to further explore the relationship between fatigue and other measures of motivation and effort.

Another limitation is the somewhat vague nature of self-reported fatigue. Self-reported fatigue does not represent a unitary construct with easily identifiable causes. It is likely caused by multiple normal and disease-related processes, including central nervous system dysfunction, disability level, emotional difficulties, medication use, and sleep disturbance. Moreover, the measurement of fatigue subtypes is fraught with potential confounds. For instance, although the FIS overtly measures physical, cognitive, and social fatigue, there is relatively little factor analytic research to support the distinct nature of these constructs. Consequently, it may be useful for future studies to employ multiple self-report measures of fatigue. Future studies should also include measures of self-reported cognitive difficulties to explore the relationships among RTV, cognitive fatigue, and self-reported cognitive dysfunction. Given the potential overlapping nature of these constructs, RTV may be related to both self-reported cognitive fatigue and self-reported cognitive dysfunction. One final limitation of the present study is the use of a self-report measure of disability progression. The future uses of an objective EDSS may help clarify the observed associations among RVT, physical fatigue, and disease progression.

In summary, this study found a strong relationship between an objective behavioral measure and self-reported cognitive fatigue in MS patients. Results provide insight into the underlying cognitive mechanisms associated with self-reported fatigue and open the door for the use of new methodologies in the study of cognitive fatigue in MS. This is also the first study to find a difference between MS patients and controls on a measure of RTV. Additional study of RTV among patients with MS may provide useful information regarding the theoretical underpinnings and interplay of effort, self-reported fatigue, and neuro-psychological dysfunction. Moreover, the identification of methods to objectively quantify fatigue may eventually prove useful in clinical practice to help substantiate, reinforce, and corroborate patients' subjective report of functional difficulties.

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