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The relationship between subjective reports of fatigue and executive control in Multiple Sclerosis

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Abstract

Previous studies failed to show a relationship between fatigue and cognitive performance. We used a theory-based Delayed Item Recognition (DIR) paradigm to examine the hypothesis that subjective reports of fatigue and executive control processes were related in MS. Participants were 20 individuals diagnosed with definite diagnosis of MS with Relapsing-Remitting course and 20 controls case matched for age, sex, education and IQ. The DIR paradigm manipulated executive demands in three conditions: Alone, Partial Interference (PI), and Complete Interference (CI). Fatigue was assessed using the Fatigue Severity Scale (FSS). Results: ANOVA Repeated measures analyses showed that DIR performance was slower and less accurate as a function of MS and increased executive demands across the three task conditions. Separate linear regressions revealed that fatigue was related to DIR reaction time and accuracy performance only in the CI condition where executive demands are maximized, and only in the MS group. The present study provided first behavioral evidence that fatigue and executive control are uniquely related in MS.

Keywords

Multiple Sclerosis; Executive Control; Fatigue; Cognitive Function

Introduction

Fatigue is a multi faceted symptom that includes both cognitive and physical components. In Multiple Sclerosis (MS), a chronic neurological disease characterized by demyelination, axonal loss [1] and grey matter atrophy [2], fatigue reportedly affects between 80-95% of the population [3,4]. Fatigue may be the most common [5] and debilitating [6] symptom in MS and is a predictor of unemployment [7]. Hence, identifying mechanisms of fatigue is paramount as a prelude for risk assessment and interventions. A distinction has been made between peripheral and central fatigue [8]. While several causes for the former were identified, mechanisms of the latter remain poorly understood [9]. Moreover, there is no conceptual framework or definition of fatigue that is universally accepted [10].

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It is noteworthy that most clinical assessments of fatigue are based on subjective reports. Self reports of fatigue correlate with depression [11-13] and anxiety [14] but not with objective measures of disease severity duration or course [9,14-18]. Further, whereas fatigue correlates with perceived cognitive dysfunction [19] previous research failed to demonstrate meaningful associations between subjective reports of fatigue and a wide range of neuropsychological measures [19-22] (for review see [23]). The lack of association between subjective reports of fatigue and cognitive performance may be attributed to the following: A) the cognitive tests used were not sensitive to fatigue. B) the tests used were multi-factorial requiring cognitive abilities that were both sensitive and insensitive to fatigue. C) Multiple tests with varying degrees of difficulties and sensitivity to fatigue were used without taking into account confounders such as test order effects. D) Subjective reports of fatigue and cognitive performance are not related in MS.

Functional imaging studies suggested that the pre-frontal basal ganglia circuitry may be a core mechanism in central type fatigue seen in patients with MS [9,24-26]. This brain circuitry also subseves the executive functions [27,28] that are impaired in MS [29]. Accordingly, we hypothesized that specific measures that experimentally manipulate executive demands would be associated with self reports of fatigue in patients with MS. Executive control was assessed using dual-task methodology [30,31]. A computerized Delayed Item Recognition (DIR) task adapted from the Sternberg paradigm [32,33] served as the primary visual task. A computerized digit span test served as the secondary verbal interference task. The degree of temporal overlap between the visual and verbal tasks was experimentally manipulated in two separate dual-task conditions so that the interference with the primary task was either partial or complete. The findings, theoretical and methodological issues pertaining to this dual-task paradigm were previously discussed in details [34]. Further, validation of the paradigm and the increased executive demands in the complete interference condition were provided in a separate study [35]. Herein, we hypothesized that a relationship between subjective reports of fatigue and cognitive performance would emerge as a function of increased executive demands vis-à-vis the DIR paradigm in MS patients but not in healthy controls.

Materials and Methods

Participants

The MS patients (n=20) were recruited from the Multiple Sclerosis Center at Holy Name Hospital in Teaneck, NJ. A definite diagnosis of MS with a Relapsing-Remitting course was ascertained by the treating neurologist using the McDonald criteria [36]. Controls (n=20) were case matched on age, sex, and education. The participants were in the age range of 25 and 55 years, had adequate vision (20/40 or better) and hearing as determined in the neurological examination. Exclusion criteria were severe hand tremor, other CNS diseases and/or injuries, and clinical depression. Also, participants could not use steroids or cholinesterase inhibitors within 30 days prior to testing. All the participants consented to participate in this study and were compensated for their effort. The study was approved the IRB of the hospital and the Albert Einstein College of Medicine, Bronx, New York.

Clinical Measures

Wechsler Abbreviated Scale of Intelligence (WASI) [37] provided estimates for verbal and performance scales IQ.

The Fatigue Severity Scale (FSS) [38] assessed subjective reports of fatigue. The FSS is a 9 item self report rating scale of fatigue severity that has been found to be reliable and valid in MS.

The Beck Depression Inventory Second edition (BDI-II) [39] assessed depressive symptoms. The BDI-II is a 21 item Likert-type format self report scale that has been widely utilized to assess depression in MS [40].

Incapacity Status Scale (ISS) is 16-item, 5 point (0-4) ordinal rating scale of functional disability in MS. The ISS was developed as part of the Minimal Record of Disability in MS [41], and has been widely utilized [42]. ISS ratings were conducted by a MS specialty neurologist or nurse, and extracted from the patient's medical chart. A summary score across the 16 rated items was used to measure overall disability level.

Executive control measures

The executive control paradigm was described in details in previous studies [34,35]. However, a brief description concerning the paradigm and the administration procedures is provided below. Executive control was assessed using dual-task methodology [30,31]. A computerized Delayed Item Recognition (DIR) task adapted from the Sternberg paradigm [32,33] served as the primary visual task. A computerized digit span task served as the secondary verbal interference task. The primary visual DIR task was administered alone and in two separate dual-task conditions.

Apparatus

A Macintosh iBook computer, with a 12.1-in. (31.3-cm) diagonal viewable monitor was used to administer the single and two dual tasks using PsyScope software [43]. Visual stimuli were presented on the computer screen. Keys on the left and right sides of the keyboard served as response keys for the DIR task. Auditory stimuli for the Digit Span Test were digitized voice recordings played by the computer and amplified by digital speakers. The single and two dual-task conditions are presented schematically in Figure 1.

Task Procedures

All training and testing procedures were conducted in the same laboratory room in the medical center and completed on the same day. Each trial of the DIR task consisted of set presentation, retention delay and probe presentation. Stimulus set size was two. The non-verbal stimuli consisted of 450 different computer-generated closed-curve shapes. Each shape was presented only once in the testing conditions of each participant. There were four experimental blocks each consisting of 10 trials with 5 true positive and 5 true negative probes yielding a total of 40 trials for the entire task per participant. The participants indicated whether the probe item was included in the initial set by a differential button press. The participants were instructed to respond as quickly and as accurately as possible.

A computerized digit span served as the interference task. It consisted of auditory presentation and verbal recall of five-digit sets. The participants listened to a set of five numbers, produced by the computer at a rate of one digit per second. They were then asked to repeat the digits in the same order and at the same pace. The times at which each digit was produced was monitored by the computer. The accuracy of the digit recall was hand-recorded by the tester. The computerized digit span task was administered alone and in the two dual-task conditions.

The two dual-task conditions consisted of 40 DIR trials each as well. In the partial interference condition (PI) overlap was limited to the retention phase of the DIR task. In the complete interference condition (CI) overlap was extended to the set presentation, retention, and probe phases of the DIR task.

Training on the individual and dual-task conditions always preceded the testing conditions. In the testing phase, the administration order of the single and two dual-task conditions was randomized to eliminate practice effects.

Statistical Analyses

Demographic characteristics, WASI indices, Fatigue, Depression, functional disability, and performance on the executive control paradigm were tabulated for descriptive purposes. Repeated measures General Linear Model (GLM) assessed the effect of group (MS vs. control) task (three-level within subject variable) and group × task interaction on DIR task performance. Dependent measures were mean reaction time (milliseconds) for correct trials only and accuracy (number of correct trials). To assess associations between fatigue and cognitive performance on the DIR task regression analyses were run separately for the MS and control groups. Separate linear regressions using the simultaneous entry method assessed whether fatigue scores were associated with performance on the single and two dual-task conditions of the DIR task. Dependent measures were reaction time and accuracy on the DIR task. Given the age range within each group and the possible confounding effects of depression and functional disability on associations between executive control and fatigue analyses controlled for chronological age, BDI –II and ISS scores.

Results

The MS and control participants were matched on age, sex, and education. Estimates of verbal and performance IQ were comparable across the two groups (see Table 1). There were 18 females in each group.

As expected, fatigue and depression scores were higher in the MS compared to the control group. However, the range of scores on these measures was comparable in the two groups. Descriptively, DIR performance was slower and less accurate in the MS group compared to the controls across the three task conditions (Table 1).

Repeated measures ANOVA examined the effect of group (between-subjects factor) and task condition (3-level within-subjects variable) on mean DIR reaction time. Main effects were significant for group $F(1, 38) = 15.12$, $p < .0001$ and task $F(2, 76) = 9.2$, $p < .0001$. The two-way interaction of group and task was not statistically significant $F(2, 76) = 1.99$, $p = .143$. Planned contrast analyses showed that compared to the alone condition reaction time was significantly slower in the CI dual-task condition $F(1, 38) = 6.4$, $p = .015$. The difference in performance between the alone and PI dual-task conditions was not significant $F(1, 38) = 2.7$, $p = .109$.

Separate repeated measures ANOVA examined the effect of group (between-subjects factor) and task condition (3-level within-subjects variable) on DIR accuracy. Main effects were significant for group $F(1, 38) = 8.85$, $p=.005$ and task $F(2, 76) = 11.8$, $p < .0001$. The two-way interaction of group and task was not statistically significant $F(2, 76) = .198$, $p = .820$. Planned contrast analyses showed that compared to the alone condition accuracy was significantly lower in the CI dual-task condition $F(1, 38) = 19.9$, $p < .001$. The difference in accuracy between the alone and PI dual-task conditions was not significant $F(1, 38) = 1.05$, $p = .311$.

Separate linear regressions examined the associations between fatigue and DIR performance (reaction time and accuracy) in the alone and two dual-task conditions within each group adjusting for the effects of chronological age, BDI-II, and ISS scores (see Table 2).

Table 2 reveals that associations between FSS scores and DIR performance (reaction time and accuracy) were significant in the CI dual-task condition but only in the MS group. In contrast, BDI-II scores were associated with DIR performance in the alone condition in the MS group. Chronological age was associated with DIR performance in the PI and CI conditions in the control group.

In secondary analysis, reaction time in the CI condition was orthogonalized with respect to reaction time in the alone condition of the DIR task. We then examined the relationship between fatigue and the orthogonalized CI reaction time measure. This analysis was designed to address the possibility that reduced speed of processing in MS but not increased executive demands accounted for the association between fatigue and reaction time in the CI condition. Linear regression using the simultaneous entry method with FSS scores as the predictor, adjusting for age, BDI-II and ISS scores, and the orthogonalized CI measure as the outcome variable was statistically significant (standardized β=.764, t=3.4, p=0.004).

Discussion

The present paper examined whether associations between subjective reports of fatigue and executive control could be identified in patients with MS. It is noteworthy that previous studies using a wide range of neuropsychological measures failed to demonstrate a relationship between fatigue and cognitive performance [23]. However, in contrast to previous research the authors used a single theory-based working memory paradigm that experimentally manipulated executive demands across three task conditions [34,35]. The findings revealed an informative relationship between fatigue and cognitive performance that was evident as a function of increased executive demands, and only in the MS patients.

It was important to demonstrate that the relationship between executive control and fatigue was not confounded by decreased speed of processing in MS. As previously mentioned we used a single paradigm with three task conditions that manipulated executive demands but were identical in terms of motor execution. The relationship between fatigue and executive control emerged only in the complete interference (CI) condition where executive requirements are maximized. We used reaction time and accuracy as indices of cognitive performance across the three DIR task conditions and found the same effect. This level of consistency across outcome measures provides converging evidence in support of the association between fatigue and executive control. In addition, we orthogonalized the CI reaction time performance with respect to reaction time in alone condition of the DIR task. The relationship between the orthogonalized reaction time CI measure and fatigue remained significant. This finding further suggests the relationship between variability in performance in the CI condition and fatigue was related to executive demands and not to general reduction in speed of processing in MS.

Evidence from imaging studies suggests that the frontal basal ganglia circuitry may underlie central fatigue in MS [24,26]. Atrophy in the frontal striatal system was reported in MS [44] and related to cognitive impairment [45,46]. The pre-frontal cortex subserves executive control processes [27,28], and has functional connectivity to the Striatum [47]. Hence, the associations between reports of fatigue and executive control reported herein, although absent from previous research, are theoretically sound and biologically plausible. It is noteworthy that the association between executive control and fatigue was not significant in the case-matched healthy controls. This lack of association cannot be attributed to restricted range in the variables of interest. Although fatigue and depression scores were significantly lower and DIR task performance was significantly better in the controls compared to the MS patients, the range of scores on those measures was comparable across groups. Thus it appears that the association between executive control and fatigue in the MS group is likely attributed to disease-related pathology in neural substrate mediating both functions. However, objective measures of cortical atrophy

and activation are necessary to substantiate this contention. It is noteworthy that the analyses revealing associations between fatigue and executive control adjusted for functional disability, estimated by the ISS, as well. The relatively low ISS scores were also related to DIR performance in the CI condition where executive demands are maximized. Therefore it appears that executive control was also sensitive to the relatively mild disease burden observed in this MS sample.

Fatigue and depression were differentially related to cognitive performance on the DIR task in MS. Whereas fatigue scores were associated with performance in the complete interference condition, depression scores were related to performance in the alone condition. This dissociation is noteworthy, especially given the high correlation between fatigue and depression in this MS sample ($r=.661$, $p<0.01$) and in other studies [11-13]. Our previous study showed that memory was the most potent predictor of performance differences on the DIR task when performed alone whereas attention and executive function predicted performance differences in the complete interference condition of the DIR task [35]. Hence, the association between depression scores and DIR performance in the alone condition is consistent with a large corpus of research showing that depression and memory co-occur and share neural substrate in mood disorders [48] and in MS [49]. As discussed earlier, the frontal basal ganglia circuitry that is implicated as the neural substrate underlying central fatigue also subserves executive control. Thus, the differential behavioral effects of depression and fatigue on DIR task performance have a plausible biological basis.

The association of chronological age with cognitive performance in the complete interference condition in the healthy controls is consistent with a large corpus of research documenting the deleterious effect of aging on executive function [34]. The effect of chronological age on DIR performance was not significant in the MS group. It is likely that disease burden in the MS patients served as a proxy for aging and its negative effect on cognitive performance.

The limitations of the study should be considered. The sample was relatively small and homogeneous in terms of its ethnic and gender composition. Also, the functional disability and level of cognitive impairment in the MS sample were relatively mild. Thus, the generalizability of the findings reported herein to other MS samples should be examined in future studies.

In summary, the present study provided first behavioral evidence to the hypothesis that subjective reports of fatigue and executive control processes were related in MS. These findings are consistent with the putative role the pre-frontal basal ganglia circuitry has in mediating central fatigue. Future studies should use refined cognitive paradigms and functional imaging in concert to confirm these findings.

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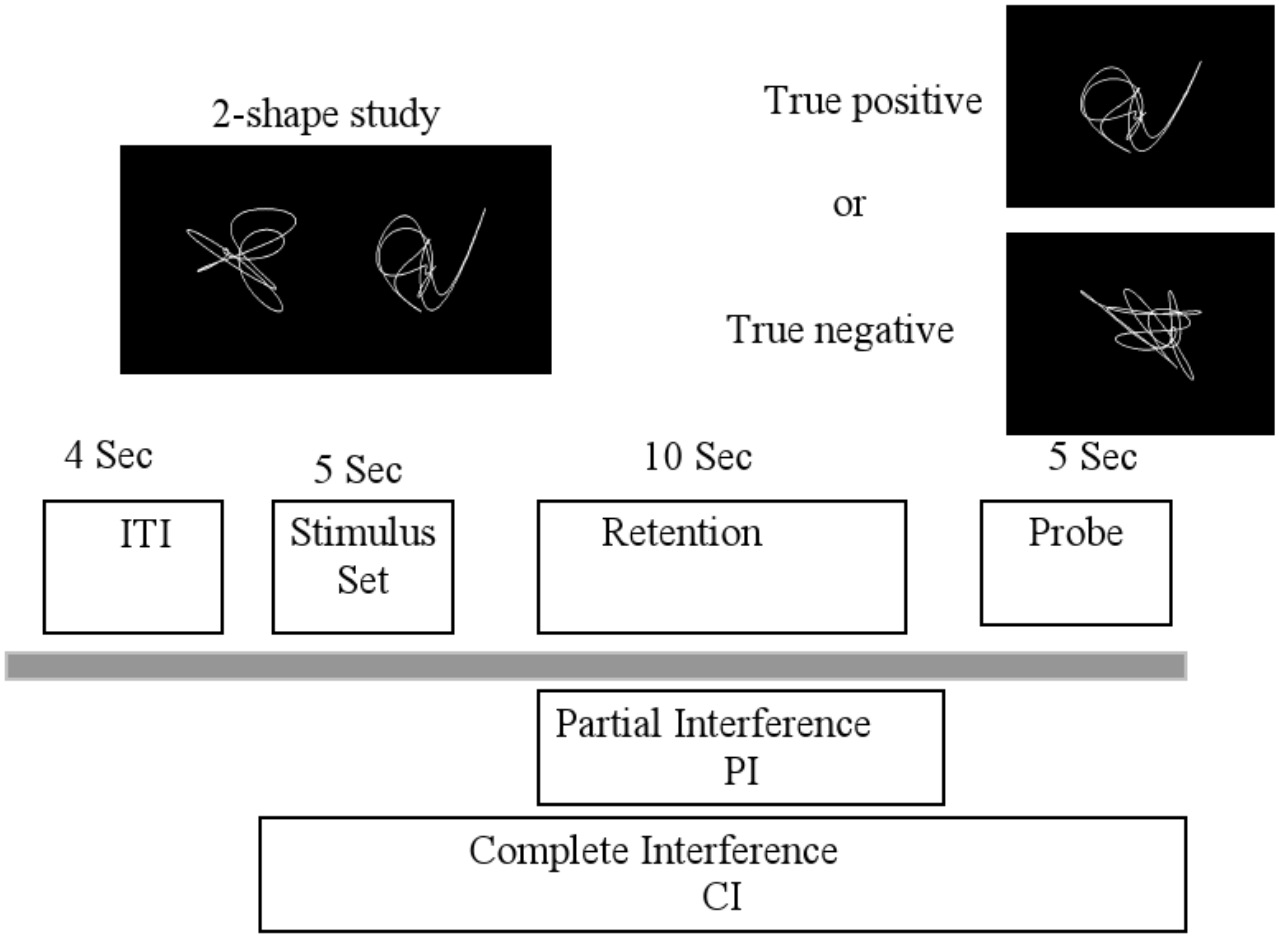

Figure 1.
Schematic presentation of the DIR Task in the alone PI and CI conditions (Number of trials per task condition = 40)

Table 1

Demographic characteristics and cognitive neuropsychological performance of the MS patient and case-matched healthy controls

	Controls (n=20)		MS (n=20)	
	M	**SD**	**M**	**SD**
Age (years)	39.90	9.1	40.55	8.6
Education (years)	16.25	1.7	15.85	2.3
WASI VIQ	111.4	10.6	110.4	18.9
WASI PIQ	106.1	12.5	103.9	15.1
FSS*	26.15	10.9	44.0	10.5
BDI-II*	4.10	4.9	10.4	8.1
ISS	--	--	7.2	4.8
DIR alone (RT)	1364	318	1713	369
DIR PI (RT)	1328	262	1595	328
DIR CI (RT)	1462	378	1969	544
DIR alone (accuracy)	34.2	2.4	30.4	4.2
DIR PI (accuracy)	36.3	8.8	31	7.7
DIR CI (accuracy)	30.1	5.5	26	7.3

Independent-samples *t* tests (*df* =38) were used to examine group differences (MS vs. Controls) on all continuous covariates.

WASI= Wechsler Adult; FSS=Fatigue Severity Scale; BDI-II= Beck depression inventory 2nd edition; ISS= Incapacity Status Scale; DIR=Delayed Item Recognition RT=millisecond reaction time; accuracy=total correct trials (n=40 in each task condition); PI=Partial Interference; CI=Complete Interference

* p<.05;

** p<.01

Table 2

Linear regressions examining association of fatigue with DIR performance across the three task conditions

	DIR Alone		DIR PI		DIR CI	
	β(RT)	**β(accuracy)**	**β(RT)**	**β(accuracy)**	**β(RT)**	**β(accuracy)**
MS						
FSS	-.317	-.070	.432	-.131	**.559***	**-.405***
BDI-II	**.669***	.396	-.119	.417	-.233	.345
ISS	.151	.283	.132	.270	**.527***	.261
Age	-.166	.191	.268	.148	-.270	.198
Controls						
FSS	-.125	-.319	-.219	.221	-.371	.351
BDI-II	-.146	.076	.059	.133	-.125	-.362
Age	.301	-.306	.233	**-.486**	**.448***	**-.452***

FSS=Fatigue Severity Scale; BDI-II= Beck depression inventory 2nd edition; ISS=Incapacity Status Scale; DIR=Delayed Item Recognition; PI=Partial Interference; CI=Complete Interference

Higher accuracy scores denote better performance

Higher RT scores denote worse performance

* denotes $p<0.05$

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