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Relationships between information processing, depression, fatigue and cognition in multiple sclerosis

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Abstract

The neurobehavioral sequelae of multiple sclerosis (MS) consistently include fatigue, depression and cognitive dysfunction with slower processing figuring prominently. However, processing speed is often confounded with accuracy and the relative contributions of depressed mood and fatigue in influencing speed of processing are difficult to quantify. Therefore, there were three objectives in this study. First, compare processing speed in MS and healthy controls under conditions in which accuracy is not confounded with speed; second, determine the relationships between information processing speed and cognition; third, determine the contributions of clinical depression and fatigue in mediating these relationships. Forty-eight participants with confirmed MS participated. The findings suggested that slower processing was correlated with higher levels of depressed mood, fatigue, lower verbal fluency, fewer words and digits recalled and poorer recall of visual-spatial information. Depression and physical fatigue had the greatest influence on the association between processing speed and more effortful tasks (e.g., immediate word recall and word list learning). Current findings extend previous work by using a more sensitive measure of processing speed and by quantifying the relative contributions of depression and fatigue in mediating relationships between processing speed and cognition.

Keywords: Multiple sclerosis; Information processing speed; Depression; Fatigue; Prefrontal cortex

1. Introduction

The neurobehavioral sequelae of multiple sclerosis (MS) consistently include fatigue, clinical depression and cognitive dysfunction (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca & Johnson, 1993; Diamond, DeLuca, Johnson, & Kelley, 1997; Krupp, Christodoulou, & Schombert, 2005; Rao, Huber, & Bornstein, 1992). Major depression occurs in MS at three times the prevalence rate reported for psychiatric comorbidity in community-based samples, and it also exceeds that for other disabling neurologic disorders (Schiffer & Babigian, 1984). Generally, the literature shows

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that depression is reported at a rate of 27–54% in MS (McGuigan & Hutchinson, 2006; Minden & Schiffer, 1990; Nocentini, 2006).

1.1. Mechanisms mediating depression in MS

Depression in MS has not been linked to a family (Sadovnick et al., 1996) or individual history of affective disorder pre-dating neurological symptoms (Minden, Orav, & Reich, 1987) or disease activity, duration, severity, or type of MS (Feinstein & Feinstein, 2001; Huber, Rammohan, Bornstein, & Christy, 1993; Minden et al., 1987; Rabins et al., 1986; Shnek, Foley, & LaRocca, 1997). Benedict, Carone, and Bakshi (2004) have reported that in MS cerebral atrophy and lesion burden are correlated with mood, cognitive dysfunction and personality disturbances and that both euphoria and disinhibition are predicted by atrophy (with executive dysfunction thought to mediate this relationship). However, there could be an alternative explanation. That is, cerebral atrophy is associated with greater cognitive and physical disability which would, therefore, cause more emotional distress and depression. Relatedly, in healthy participants, a reduction in perfusion of dorsolateral prefrontal cortex (DPC) appears to be related to the severity of depressive symptoms, psychomotor slowing, and cognitive impairment (Grady, 1999; Mayberg et al., 1999), in addition to structural changes in gray matter volume within the prefrontal cortex, the hippocampus, and the striatum (Fossati et al., 2004).

1.2. Cognition in MS

On recognition memory, incidental recall, verbal or visual recall (Arnett, Higginison, Voss, Wright, et al., 1999) and Digit Span (Wechsler Adult Intelligence Scale-Revised (WAIS-R): Wechsler, 1981) some studies have reported no differences in performance between MS and healthy controls (DeLuca & Johnson, 1993). However, some studies have shown differences (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995). Diamond et al. (1997) using the California Verbal Learning Test (CVLT) reported that individuals with MS tended to use a less efficient serial versus semantic clustering encoding strategy compared to stroke patients and healthy controls.

Information processing speed is generally slower in individuals with MS versus healthy controls (DeLuca, Johnson, & Natelson, 1993; DeLuca & Johnson, 1993; Demaree, DeLuca, Gaudino, & Diamond, 1999; Diamond et al., 1997; Grossman, Robinson, & Onishi, 1995; Kail, 1998). Using the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1997) or a visually based computer version of the serial addition task, no disproportionate, modality-specific impairments in the MS group were reported (Johnson, DeLuca, & Natelson, 1996). Similar findings have been reported by Diamond et al. (1997), with slower processing thought to be particularly mediated by impairment in the operation of the central executive. Slower reaction and memory scanning times have been reported in both MS and healthy control groups using the Sternberg Memory Scanning Test. This task, however, eliminates the motor response component with the results suggesting that slower processing speed in MS is independent of slowed motor ability (Rao, Leo, Haughton, & St. Aubin-Faubert, 1989).

1.3. Fatigue and cognition in MS

Fatigue is a prominent symptom in MS and it has been differentiated on the basis of subjective versus objective or "cognitive fatigue" and described as a decline in cognitive performance during a task or across a testing session (Krupp & Elkins, 2000; Paul, Beatty, Schneider, Blanco, & Hames, 1998). Some researchers have reported cognitive fatigue in MS (Krupp & Elkins, 2000; Kujala, Portin, Revonsuo, & Ruutainen, 1995), while others have not (Beatty et al., 2004; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Paul et al., 1998). Moreover, studies examining short-term memory (Johnson, DeLuca, Diamond, & Natelson, 1998), attention and working memory (Bailey, Channon, & Beaumont, 2007), verbal fluency (Rao, Leo, Bernadin, & Unverzagt, 1991), and verbal memory (Paul et al., 1998; Schwartz, Coulthard-Morris, & Zeng, 1996) have failed to find a relationship between subjective fatigue and cognitive performance. While Krupp and Elkins (2000) found a decrement in MS cognitive performance compared to healthy controls over a 4-h testing session, self-reported fatigue was unrelated to the pattern of decline. In the Johnson et al. (1997) study, which induced fatigue, MS performance on the PASAT improved over repeated trials despite increased levels of self-reported fatigue. Speculation regarding the mechanisms mediating fatigue have included CNS and immune dysregulation (Krupp et al., 2005) and reduced glucose metabolism in the frontal cortex and basal ganglia (Roelke et al., 1997) with presumed impaired interaction between dorsolateral-prefrontal and motor circuits (Alexander, Crutcher, & DeLong, 1990).

1.4. Depression, cognition and information processing speed in MS

A number of studies have not reported a significant relationship between depression and cognition in MS (Fischer, 1988; Johnson et al., 1997; Litvan, Grafman, & Vendrell, 1988; Minden, Moes, & Orav, 1990). However, executive dysfunction has been reported in depressed MS patients (similar to healthy participants), (Channon & Green, 1990; Harvey, Le Bastard, & Pochon, 2004) compared to non-depressed MS patients (Arnett et al., 2001) (see also Troyer, Fisk, & Archibald, 1996). While recognition scores are not effective in differentiating depression subgroups, CVLT recall scores have been reported to be highest in healthy controls, followed by MS not-depressed and then MS depressed participants (Arnett, Higginison, Voss, Wright, et al., 1999) with similar patterns of encoding and retrieval reported in healthy participants (Brand, Jolles, & Gispen-de Wied, 1992; Otto et al., 1994). Johnson et al. (1998) reported that both MS and depressed participants were susceptible to brief distraction on a short-term memory task which appears to be in agreement with the effortful processing difficulties documented in some depressed groups (Hartlage, Alloy, Vazquez, & Dykman, 1993; Weingartner, 1981, 1986).

Kail (1998) reported that the cognitive slowing that accompanies MS is widespread and is not task specific. However, relationships between depression and cognition were not formally assessed. Generally, depressed MS patients have performed significantly worse than non-depressed MS patients on speeded, capacity-demanding attentional measures (Arnett, Higginison, Voss, Wright, et al., 1999). Similar findings have been reported in non-MS populations with depression, where progressive increases in working memory load were accompanied by significant decrements in performance at each increasing level of complexity (Harvey et al., 2004). Similarly, under minimal challenge to the phonological loop, individuals with MS have adequately maintained information in working memory (i.e., Harvey et al., 2004). However, when PASAT computation was added to a minimal challenge task, accuracy declined. This was interpreted as suggesting that working memory impairments in MS are within the central executive rather than the phonological loop (Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003).

Using a reading span task, Arnett, Higginison, Voss, Bender, et al. (1999) reported that depressed MS patients were impaired on working memory capacity compared to non-depressed MS patients. Relatedly, a meta-analysis of studies of memory impairment in MS concluded that depression was related to working memory and attentional deficits (Thornton & Raz, 1997). Using the PASAT, Arnett, Higginison, Voss, Wright, et al. (1999) demonstrated a significant difference in the performance of healthy and non-depressed MS groups in comparison to a depressed MS group. Landro, Celius, and Sletvold (2004) reported that early phase MS patients showed slowed processing speed on the Symbol Digit Modality Test (SDMT) and impairment on the PASAT, but only SDMT performance appeared to be influenced by depression.

Demaree et al. (1999) reported that while their MS group had slower processing speed they were comparable to healthy controls on accuracy when measured on the Visual Threshold Serial Addition Task (VTSAT) (an adaptive, computer-based version of the PASAT task). Recently, Legenfelder et al. (2006) reported that using the VTSAT, MS participants were able to achieve memory accuracy levels comparable to that of healthy controls, but they required significantly more processing time to do so. Importantly, in the previous two studies using the VTSAT, speed of processing was not confounded with accuracy. The current study employed the same VTSAT adaptive, computer-based program.

The overarching goal of this study was to examine the relationships between speed of processing and cognition in MS and to determine the relative contribution of fatigue and depression in mediating these relationships. Therefore, there were three objectives in the current study. First, compare processing speed in MS and healthy controls under conditions in which accuracy is not confounded with speed; second, determine the relationships between information processing speed and cognition; and third, determine the relative contributions of clinical depression and fatigue in mediating these relationships.

2. Method

2.1. Participants

Thirty-nine participants were recruited from a hospital registry in North Carolina which included approximately 1000 MS patients. The recruitment area included patients who were referred from a regional medical center, private practices and community-based clinics. Nine participants were recruited from a New Jersey chapter of the MS Society. Therefore,

Table 1
Multiple sclerosis demographics

Measures	Depressed		Non-depressed	
	M	*SD*	*M*	*SD*
Age	49.1	3.63	47.6	5.21
Education	15.8	2.34	16.4	2.98
EDSS	4.90	1.10	4.80	1.27
Duration	14.70	5.98	17.8	9.78

a total of 48 individuals with MS participated in this study. Thirty-five patients were female (73%) and 13 patients were male (27%). Fifty-one percent of the patients were taking either Betaseron, Copaxone or Avonex with Avonex the most commonly prescribed medication (26%). Two patients (4%) were taking medications for fatigue (Amantadine). The overall breakdown of the MS subgroups was: Relapsing Remitting (RR): 59%; Secondary Progressive (SP): 26%; Primary Progressive (PP): 14% and Progressive Relapsing (PR): 2%. In the MS depressed group 50% were RR, 31.8% were SP and 18.2% were PP. A relatively similar pattern was observed in the MS non-depressed group. That is, 57.7% were RR, 26.9% were SP, 11.5% were PP and 3.8% were PR.

The healthy control group was composed of students drawn from an introductory psychology class who received lab credit for their participation and volunteers from upper level university classes who received performance feedback for their participation. In order to match the MS and healthy control groups, students had to be at least 30 years old to participate. Twenty students with a mean age of 44.9 years participated. Fifteen of the participants were female and five were male. The mean education level was 15.9 years. There were no significant difference between the MS and healthy control groups with respect to age ($p = .21$) and education ($p = .79$), and there were no significant differences between the depressed and non-depressed patients on demographic variables. For a description of age, education, EDSS and illness duration in MS refer to Table 1.

2.2. Inclusion criteria

The study recruited males and females between 23 and 55 years of age diagnosed with clinically definite MS as defined by Poser criteria (Poser et al., 1988). Patients with a disease duration of 5–20 years who had been diagnosed for more than 2 years were recruited so that acute reactions to the diagnosis of MS was minimized. Patients with EDSS (Kurtzke, 1983) scores of between 1.5 and 6.0 were recruited. Participants were chosen on the basis of having no significant health problems other than MS and were selected from all MS disease course classifications.

2.3. Exclusion criteria

Exclusion criteria included a history of diagnosis with Bipolar disorder (Cavanaugh, 1984), Unipolar depression, ADHD, any neurological disease other than MS and cardiovascular disease. Participants were also excluded if they had a history of alcohol or drug abuse, severe motor or visual impairment that may interfere with cognitive testing, pre-morbid history of learning disability or a loss of consciousness episode lasting longer than 5 min. Participants were excluded if they experienced an exacerbation within a 1-month window of time from the date of testing.

2.4. Materials

The neuropsychological measures selected for inclusion in this study represented exemplars of a subset of cognitive domains and operations that included immediate and delayed verbal and visual memory, word list learning and recall, attention and concentration, executive function, speed of retrieval from long-term phonologic/semantic storage and information processing speed. The goal was to identify relationships between mood, fatigue, processing speed and select cognitive operations.

2.5. Depression

Center for Epidemiological Studies of Depression Scale (CES-D) The CES-D is a 20 item self-report that measures current depressive symptomatology. This measure has been constructed and validated for use in the general population (Radloff, 1977). The CES-D measures depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor slowing, loss of appetite and sleep disturbance. Diagnosing depression in MS can be complicated by a number of possible confounds including the effects of interferon beta-1b (Neilley, Goodin, Goodkin, & Hauser, 1996) and scales with disproportionate weighting of vegetative and somatic items (i.e., BDI) that can overlap with MS symptoms and, therefore, overestimate depression in MS (Johnson et al., 1996; Nyenhuis et al., 1995).

The CES-D scale minimizes the physical symptoms that overlap with MS symptoms. Responses are based on a four-point Likert scale (0 = rarely or none of the time and 3 = most, or all of the time). Cut-off scores of 16 have been used to screen for clinical depression in community samples (Roberts & Vernon, 1983) and are traditionally interpreted as suggestive of clinically significant depression (McDowell & Newell, 1996). Moreover, the CES-D has exhibited good predictive value in identifying MS patients who have depressive disorder. For example, of 47 MS patients who scored $\geq$16 on the CES-D, 74.5% ($n = 38$) were found to have a depressive disorder (Pandya, Metz, & Patten, 2005).

2.6. Fatigue

Modified Fatigue Impact Scale (MFIS)—21-item scale assessing the impact of fatigue on cognitive, physical and social domains (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994).

2.7. Neuropsychological assessments

2.7.1. California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987)

The CVLT is a measure of both recall and recognition of word lists presented over a number of trials. The test provides measures that include: immediate and delayed memory, semantic and serial learning strategies, serial positioning effects, learning rate across trials, consistency of item recall across trials, degree of vulnerability to proactive and retroactive interference and delayed recognition (hits minus false positives) which has been conceptualized as requiring only automatic processing capability (Arnett, Higginison, Voss, Wright, et al., 1999). Recognition performance is generally intact in depressed MS and in healthy populations and the current study is in agreement with previous findings (MS: $M = 14.9$, $SD = 1.2$, healthy controls: $M = 15.2$, $SD = 1.0$, $t(66) = 1.07$, $p = .29$).

CVLT-Trial 1, List A, CVLT-T1-5 and CVLT-Long Delayed Free Recall were included in the analysis as representative of effortful immediate verbal encoding and recall, word list learning and recall and delayed verbal recall tasks, respectively. The CVLT-Trial 1 List A task was viewed as providing a baseline measure of encoding and immediate recall that is less influenced by encoding and retrieval strategies as well as word repetition effects.

Digit Span: (Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981).

The Digit Span is used to measure immediate memory span. The dependent measures are total forward digit span and total backward digit span.

2.7.2. Controlled Oral Word Association Test (COWAT)

The COWAT (Benton & Hamsher, 1989; Benton, Sivan, Hamsher, Varney, & Spreen, 1994) is a test of verbal fluency in which subjects are asked to say as many words as they can think of beginning with the letters "F, A, and S", or "C, F, and L" within 1 min. The dependent measure is the total number of words produced. The COWAT has been used to detect deficits in verbal communication and assess communication ability in everyday life (Loonstra, Tarlow, & Sellers, 2001). Beatty, Goodkin, Monson, and Beatty (1989) have reported MS verbal fluency impairment relative to healthy controls. The present study included the COWAT in order to explore its potential for differentiating MS depressed, non-depressed and healthy control groups. Moreover, since the COWAT is a timed task, it was hypothesized that it would be more demanding for depressed MS participants.

2.7.3. Rey–Osterreith Complex Figure Test (ROCFT)

The ROCFT is a test that assesses visual perceptual-motor integration skills, organizational skills and immediate and delayed visual-spatial recall.

2.7.4. Visual Threshold Serial Addition Test (VTSAT)

All subjects were administered the VTSAT in accordance with previously published procedures (Diamond et al., 2000). The VTSAT presents a series of 50 digits sequentially on a computer monitor. Similar to the PASAT, subjects were instructed to add each single digit number presented (i.e., ranging from 1 to 9) to the number immediately preceding it and report the sum aloud. The numbers were presented centrally on the computer monitor and were 5 mm in height. In contrast to the traditional PASAT which relies on four different but fixed inter-stimulus intervals, the VTSAT program uses a method of limits to compute a threshold or inter-stimulus interval based on performance accuracy. In other words, the program uses algorithms that adjust the speed of presentation to a level that supports a performance accuracy of 50%. This level represents the threshold and is an index of processing speed (i.e., while controlling for performance accuracy). A higher score indicates a slower processing speed.

The VTSAT is a test that taps processing speed, working memory and sustained attention. It was thought that given the capacity-demanding and effortful requirements of this task, it would have a greater likelihood of being sensitive enough to differentiate depressed MS from non-depressed MS and healthy control groups.

2.8. Design

A multiple linear regression analysis using a stepwise technique examined the relationships between the dependent variable information processing speed (VTSAT) and the predictor variables: depression (CES-D), verbal fluency (COWAT), verbal encoding and immediate recall (CVLT-Trial 1), fatigue (MFIS-Total) and Digit Span (Total Digits-Scaled Scores) (DS Scale). A Multivariate analysis of variance (MANOVA) was performed with between group measure depression (Group 1 = MS depressed; Group 2 = MS non-depressed; and Group 3 = healthy controls) and dependent measures VTSAT, COWAT, MFIS-Total and the CVLT T1. In order to determine the relative impact of mood and fatigue on the relationships between cognition and processing speed, partial correlations were computed for a variety of cognitive measures. A t test was used to evaluate CVLT-Delayed Recognition in the MS ($M = 14.9$, $SD = 1.2$) and the healthy control group ($M = 15.2$, $SD = 1.0$) $t(66) = 1.07$, $p = .29$.

3. Results

3.1. Relationships between processing speed, cognition and mood

A multiple linear step-wise regression showed that there were significant correlations between the predictor variables: mood (CES-D), ($r = .396$, $p = .001$); verbal fluency (COWAT), ($r = -.467$, $p = .001$); verbal encoding and immediate recall (CVLT-List A, Trial 1), $r = -.31$, $p = .005$; CVLT-Long Delay Free Recall (CVLT-LDFR), $r = -.28$, $p = .04$; fatigue (MFIS-Total Score), ($r = .369$, $p = .001$); Digit Span (Total Digits-Scaled Scores) (DS Scale), ($r = -.45$, $p = .01$) and the dependent variable information processing speed (VTSAT). The multiple correlation between the selected predictors, COWAT and MFIS-Total and processing speed was .54. (ANOVA: $F(2, 64) = 13.26$, $p = .001$). The β values for the COWAT (−.406) and the MFIS-Total measure (.281) were significant ($t = -3.77$, $p = .001$ and $t = 2.61$, $p = .01$, respectively). The excluded CES-D variable had a β value of .268 ($r^2 = .078$) which was significant ($t = 2.38$, $p = .02$). The MFIS-Physical subscale was the component of the fatigue measure most strongly associated with processing speed, $r = .395$, $p = .01$.

These results indicate that slower information processing was associated with more depressed mood or higher scores on the CES-D; lower verbal fluency; fewer words learned and remembered on immediate recall, higher levels of fatigue (Physical subscale) and fewer digits recalled. Overall, the COWAT, MFIS-Total and CES-D measures accounted for about 51% of the variance in predicting information processing speed.

3.2. Mood, cognition and fatigue

A Multivariate Analysis of Variance (MANOVA) with between group measure depression (Groups 1–3) and dependent measures VTSAT, COWAT, MFIS-Total and the CVLT-T1 showed a significant effect $F(10) = 4.3$, $p = .001$. A

Table 2
Groups: multiple sclerosis depressed, multiple sclerosis non-depressed, and healthy control

Measures	Depressed groups	*M*	*SD*	Significance	*N*
CVLT-T1	MS depressed	51.90	8.44	1 and 3, $p = .01$	21
	MS non-depressed	51.62	8.65	2 and 3, $p = .01$	26
	Healthy control	64.90	6.51		20
CES-D	MS depressed	23.24	8.16	1 and 2, $p = .05$	21
	MS non-depressed	8.15	5.57	1 and 3, $p = .05$	26
	Healthy control	6.75	5.02		20
VTSAT	MS depressed	2130.47	85.60	1 and 3, $p = .001$	21
	MS non-depressed	1900.69	106.84	2 and 3, $p = .007$	26
	Healthy control	1200.45	42.91		20
COWAT	MS depressed	36.57	10.61	1 and 3, $p = .005$	21
	MS non-depressed	39.73	11.82	2 and 3, $p = .040$	26
	Healthy control	46.35	9.24		20
MFIS_TOT	MS depressed	47.57	17.92	1 and 3, $p = .001$	21
	MS non-depressed	41.85	13.43	2 and 3, $p = .001$	26
	Healthy control	22.35	12.18		20

Significance = multiple planned comparisons (post hoc: LSD) between groups. Group 1 = MS depressed; Group 2 = MS non-depressed; Group 3 = Healthy control. Groups 1 and 2: NS.

between subjects analysis showed that among the three groups, significant differences existed on all of the measures: VTSAT, $F(1) = 12.0$, $p = .001$; MFIS-Total, $F(1) = 22.8$, $p = .000$; COWAT $F(1) = 9.3$, $p = .003$ and CVLT T-1 $F(1) = 42.1$, $p = .01$ (see Table 2).

A multiple planned comparison (post hoc: LSD) showed that there were significant differences between MS depressed/MS non-depressed and the Healthy Control group. However, there were no significant differences between the MS depressed and MS non-depressed groups (see Table 2).

3.3. MS depressed versus a non-depressed, low CES-D subgroup

The finding of no significant difference between the MS depressed and MS non-depressed group may suggest that while having MS affects information processing speed, depressed mood may not be associated with disproportionate reductions in processing speed. However, a comparison of processing speed in the MS depressed group (CES-D: $M = 23.2$, $SD = 8.1$) (VTSAT: $M = 2190.2$, $SD = 87.8$, $n = 22$) with an MS non-depressed, low CES-D subgroup (CES-D: $M = 4.0$, $SD = 1.15$) (VTSAT: $M = 1630.69$, $SD = 44.63$, $n = 13$) showed that the subset of individuals with low CES-D scores processed information more rapidly than individuals with higher CES-D scores $F(1) = 4.47$, $p = .042$. Moreover, there were no significant differences between the MS depressed and the low CES-D subgroups with respect to physical fatigue (MFIS-Physical) (NS).

3.4. Processing speed and cognition: contributions of mood and fatigue

With the effects of mood (CES-D) partialed out, there were reductions in correlations between processing speed and the following measures: CVLT-T1, $r = -.24$, $p = .04$ (23% reduction); DS Scale, $r = -.39$, $p = .001$ (13% reduction) and COWAT $r = -.38$, $p = .001$ (17% reduction). When the effects of both mood *and* physical fatigue were partialed out, there was only a modest impact on the correlations, except for the CVLT-T1 measure, $r = -.13$, NS (58% reduction).

A Pearson correlation revealed a significant association between mood and processing speed ($r = .43$, $p = .01$) (with CES-D scores accounting for 18% of the variance). However, when the effect of physical fatigue was partialed out, there was a reduction in the correlation to $r = .28$. In other words, mood accounted for about 8% of the variance in processing speed after physical fatigue was partialed out (i.e., physical fatigue accounted for ∼10% of the variance).

A correlation also revealed a significant association between processing speed and CVLT-T1-5, an effortful word list learning and recall task ($r = -.36$, $p = .003$). However, when the effect of mood was partialed out, the association between processing speed and CVLT-T1-T5 was reduced to $r = -.24$ and when physical fatigue was partialed out, the

correlation was reduced to −.12. In other words, mood and fatigue accounted for about 66% of the variance between processing speed and word list learning and recall. There was also a significant association between processing speed and Rey Immediate ($r = -.46$, $p = .03$) ($M = 16.5$, $SD = 8.0$) and Delayed Recall ($r = -.68$, $p = .01$) ($M = 16.5$, $SD = 7.5$). However, in contrast to immediate and delayed verbal recall, when the effects of mood and physical fatigue were partialed out, the associations between processing speed and Rey Immediate ($r = -.59$, $p = .006$) and Delayed Recall ($r = -.71$, $p = .01$) were not reduced.

3.5. Conclusion and discussion

Slower information processing was correlated with higher levels of depressed mood and fatigue, lower verbal fluency, fewer digits recalled from immediate memory, fewer words recalled from immediate and long-term memory and poorer immediate and delayed recall of complex visual information. In other words, there was an association between speed of processing and the efficiency with which words were recalled from long-term storage (i.e., COWAT) and verbal and visual information was encoded and recalled from immediate and delayed memory.

In an effort to determine the impact of mood and fatigue on processing speed and cognition, a partial correlation showed that when mood was partialed out, there was a reduction in the strength of the association between speed of processing and word recall, digit recall and word fluency. While the combined effect of depressed mood *and* fatigue on the strength of the association between processing speed and cognitive measures appeared to be modest, immediate word recall and word list learning and recall were exceptions. That is, when the physical fatigue measure was partialed out, there was a 58% reduction in the strength of the association between processing speed and immediate verbal recall and when mood and fatigue were both partialed out, they accounted for about 66% of the variance between processing speed and performance on the effortful word list learning and recall task (CVLT-T1-5). Taken together, the data may suggest that information processing speed is predictive of performance in verbal and visual-spatial tasks that involve effortful processing. Moreover, verbal encoding and recall appeared to be influenced by a combination of processing speed, depressed mood and fatigue.

There were no overall differences between the MS depressed and MS non-depressed groups with respect to mean scores on cognitive measures. This finding may be accounted for by the fact that by extracting mood scores with greater separation, the sensitivity of the relationship between cognition and depressed mood was enhanced. Support for this idea is provided by the finding that an MS non-depressed subgroup with very low CES-D scores processed information more rapidly than the MS depressed group. The differences in processing speed could not be attributed to fatigue as the two groups showed no significant differences with respect to their physical fatigue subscale scores. This is important given the finding that processing speed (VTSAT) and fatigue (MFIS-Physical subscale) were correlated.

The results of the present study corroborate those of Arnett, Higginison, Voss, Wright, et al. (1999), Arnett, Higginison, Voss, Bender, et al. (1999) and Landro et al. (2004) who also found processing is slower in MS depressed compared to non-depressed MS groups. However, our results extend those findings by showing that using a computer-based, adaptive processing speed task that equated performance accuracy across groups, varying levels of CES-D scores were associated with variable speeds of information processing. When speed is confounded with accuracy, it is difficult to determine whether patterns of performance are attributable to deficits in accuracy or speed. In the current study, with accuracy controlled, processing speed could be measured more accurately.

The current findings also extend previous work by quantifying the relative contributions of mood and fatigue in mediating the association between speed of processing and tasks with varying levels of effortful and capacity-demanding characteristics (Hasher & Zacks, 1979). That is, mood and fatigue appeared to have the greatest impact on the effortful word list learning and recall task and on immediate verbal recall. However, in contrast to verbal learning and recall, immediate and delayed visual-spatial recall did not appear to be as vulnerable to the effects of fatigue and mood. The differential impact of mood and fatigue on verbal and visual-spatial recall may be related to well-established impairments in verbal recall and word fluency in MS and to the likelihood that verbal encoding and recall are more capacity-demanding than visual-spatial encoding and recall.

With respect to mechanisms that may mediate the linkage between depression and information processing, the imaging literature reports an association between depression and reduced perfusion in the DPC. Given the putative role played by the DPC in information processing, it may suggest that with the increasingly reduced cerebral perfusion accompanying more severe depression, information processing and performance on capacity-demanding cognitive tasks would be adversely affected.

Overall, these findings provide support for associations between mood and processing speed and for the influence of processing speed, mood and fatigue on cognition. Moreover, these findings also provide some insight into the relative contributions of mood and fatigue on cognitive tasks that tap variable operations and that require differing levels of effortful processing. Given the prevalence of depression and fatigue in MS and the fact that several studies have found that psychological factors (particularly depression) were more important determinants of quality of life in individuals with MS than were Expanded Disability Status Scores (EDSS) (Amato, Ponziani, Siracusa, & Sorbi, 2001; Wang, Reimer, & Metz, 2000), a better understanding of the influence and impact of mood and fatigue on information processing, cognition and instrumental activities of daily living becomes even more important. The current findings suggest that clinical attention and treatment of disturbances in mood and fatigue could contribute to enhancing not only overall quality of life in MS but to the efficiency with which information is processed as well.

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