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Working Memory Impairments in Multiple Sclerosis: Evidence From a Dual-Task Paradigm

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The aim of this study was to investigate working memory in multiple sclerosis (MS) patients. To test the hypothesis that the central executive system (CES) of working memory is impaired, 36 MS patients were administered a dual-task paradigm in which a judgment of line orientation measure was performed concurrently with finger tapping, humming a melody, or reciting the alphabet. MS patients exhibited a significantly greater decrement in performance than controls during the more demanding dual-task conditions (concurrent humming or alphabet recitation) as compared with the single-task condition. Dual-task performance in MS patients correlated with performance on the Paced Auditory Serial Addition Test but not with other cognitive or clinical measures. The authors conclude that MS patients have a working memory deficit reflecting an impaired central executive system. Moreover, impairments in speed of information processing in MS patients are associated with this CES deficit.

Memory dysfunction is the most common cognitive impairment observed in patients with multiple sclerosis (MS). A long-term memory deficit in these patients is well documented (Grafman, Rao, & Litvan, 1990), but most early studies of MS patients have concluded that short-term memory (STM) is intact. Support for this claim was derived from the observation of a normal digit span, as well as an intact recency effect on supraspan list learning, measures commonly used to assess STM (Caine, Bambord, Schiffer, Shoulson, & Levy, 1986; Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984). Although most studies continue to focus on the long-term memory impairments in MS patients (Rao, Leo, & Aubin-Faubert, 1989), evidence is accumulating that STM deficits may also exist (Grigsby, Ayarbe, Kravcism, & Busenbark, 1994; Rao et al., 1993). However, the nature of these deficits remain unclear. The purpose of this study was to further investigate STM processing in MS patients.

Several experimental tasks have been useful for identifying impairment in various aspects of STM in MS patients. One experimental measure, the Brown-Peterson task (Peterson & Peterson, 1959), measures consolidation of information in STM and the effect of interference on temporarily stored information. With this task, two groups of investigators (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988; Grant, McDonald, Trimble, Smith, & Reed, 1984) found impairments in MS patients as compared with controls, suggesting a deficit in short-term storage. However, other investigators (Litvan, Grafman, Vendrell, & Martinez, 1988; Rao, Aubin-Faubert, & Leo, 1989) were unable to replicate this finding. In another study, the Sternberg paradigm (Sternberg, 1975) was used to assess the rate at which information held in STM is scanned. Rao, Aubin-Faubert, & Leo (1989) found a difference in reaction time slope between MS patients and controls, suggesting that MS patients were impaired at scanning information rapidly in STM. This difference was not due to defects in motor functioning that can also prolong reaction time performance. However, this finding was not confirmed by Litvan, Grafman, Vendrell, Martinez, Junque, et al. (1988), although demographic differences in the MS patients tested in the two studies may have accounted for the discrepant results. In summary, several experimental tasks that have been used to probe STM in MS patients have provided inconclusive results.

In this article, we adopted the approach of applying a cognitive model developed in normal subjects to the understanding of cognitive impairments in MS patients. The model for STM we have chosen is known as working memory. Extensive experimental investigations have led Baddeley (1986) to propose that working memory is not a unitary system. Instead, working memory appears to be comprised of a central executive system that regulates the distribution of limited attentional resources and coordinates information within verbal and spatial slave systems (called the phonological loop and the visuospatial sketchpad, respectively). The central executive system also controls cognitive processing when novel tasks are involved and when existing habits have to be overridden. In contrast, the slave systems are involved in passive storage of modality-specific information. In such a model, it is possible for normal slave system functioning to coexist with a defective central executive system.

Two studies have used Baddeley’s model to test directly the functioning of the phonological loop in MS patients. Even
though MS patients had a normal digit span, Litvan, Grafman, Vendrell, Martinez, Junque, et al. (1988) and Rao et al. (1993) found an exaggerated word-length effect. This finding was thought to reflect an impaired articulatory rehearsal process in the phonological loop of verbal working memory, suggesting that MS patients are restricted in the amount or duration of the information that can be held in the verbal buffer during encoding. Taken together, these reports provide considerable support for the hypothesis that at least one component of working memory is impaired in MS patients.

The present study was aimed at exploring another component of working memory in MS patients, the central executive system (CES). Because the CES is necessary to coordinate the performance of two concurrent tasks, dual-task paradigms have been designed to examine CES functioning (Baddeley, 1986). The CES is thought to have a limited capacity, and performance on a dual-task paradigm will suffer if the demands of concurrent task performance exceeds this capacity. Thus, two tasks that are performed individually or that cause relatively little interference with each other when performed concurrently will make minimal demands on the CES. However, performed together two tasks that make similar demands on the CES will lead to a decrement in performance. There is some evidence that MS patients are compromised on tasks that appear to require other forms of executive control (Beatty, Goodkin, Beatty, & Monson, 1989; Grossman et al., 1994; Rao & Hammeke, 1984). Consequently, we hypothesized that MS patients will have an impairment in the CES of working memory, resulting in a greater decrement in performance during resource demanding, dual-task conditions as compared with controls. In order to examine the relationship between the CES and other cognitive functions such as other forms of executive control, we related performance on the dual-task paradigm to several other neuropsychological measures in MS patients.

**Method**

**Participants**

We studied 36 right-handed patients with clinically definite multiple sclerosis (MS) recruited from the Comprehensive Multiple Sclerosis Center of the Department of Neurology at the Hospital of the University of Pennsylvania. The average age of the MS patients was 39.2 years (SD 8.8) and the average education was 14.8 years (SD 2.7). MS patients were compared with 15 age-matched, t(49) = 0.01, and education-matched, t(49) = 1.02, controls. The MS group consisted of 32 patients classified as relapsing-remitting (RR) and 4 patients as chronic progressive (CP). Patients with a relapsing-remitting disease were required to have had at least two relapses in the 2 years prior to entry into the study. A relapse was defined as the appearance of one or more new neurological abnormalities, preceded by a stable or improving neurologic state and lasting at least 24 hours. Patients with chronic-progressive disease were required to have had neurologic worsening documented by physical examination over the 2 years prior to entry into the study. All patients were tested when they were clinically stable. These patients were a subset of a larger cohort previously reported (Grossman et al., 1994). The average disease duration was 64.2 months (SD 56.7), and the average Kurtzke Extended Disability Status Score (EDSS; Kurtzke, 1983), was 3.5 (SD 1.9). All patients had a visual acuity that was better than 20/60 in both eyes.

**Experimental Paradigm**

The procedure for the dual-task paradigm consisted of performing a primary task concurrently with one of three secondary tasks. In the single-task condition, each participant performed the primary task alone for 30 s. In the dual-task conditions, the participant was instructed to perform both the primary and secondary tasks concurrently and as accurately as possible, also for 30 s. In the analyses, performance on the primary task was used as the dependent measure. The primary task required the participant to monitor judgment of line orientation. During this task, participants were instructed to match two lines in different orientations to an array of lines at different angles (Benton, Hamsher, Varney, & Spreen, 1983). Participants responded either orally or by pointing to the correct response. A baseline score was obtained by averaging the percentage correct over three trials.

Three nonvisual secondary tasks of varying difficulty were used: finger tapping, humming a melody, and reciting the alphabet. Finger tapping was assumed to place fewer demands on the CES than humming or reciting. By examining relative decrements of performance under different dual-task conditions, we could investigate the effects of concurrent performance of tasks with different demands, critical for the CES hypothesis. A baseline performance level was established as well for each of the secondary tasks when performed alone by averaging performance over three trials.

The tapping task required participants to tap a small lever attached to a counting device with their index finger as fast as possible during the 30-s time period allotted for performance. Separate right- and left-hand trials were used. The humming task required the participant to hum the melody of a song as often as possible during the allotted time period and the total number of notes hummed was recorded. Brahm's lullaby ("Lullaby and Goodnight") was learned prior to performance by listening to a tape and was practiced several times until the participant could correctly hum the song. Participants were encouraged not to deviate from the melody of this song during the testing. The reciting task required the participant to recite the alphabet as often as possible during the allotted time period and the total number of letters recited was recorded. Participants were instructed not to sing the alphabet song.

**Clinical Measures**

Several standard clinical neuropsychological measures were also administered to MS patients in order to correlate with their performance on the dual-task paradigm. Neuropsychological assessment also was used to rule out a generalized intellectual impairment such as a dementia. These included measures of executive function, speed of information processing, visuospatial function, and episodic long-term memory. Executive measures included the Wisconsin Card Sorting Task (WCST): categories achieved and number of perseverative responses. Sixty items were presented at a 2-s pacing for 2 min (Gronwall, 1977); and the oral form of the Symbol Digit Modalities Test (SDMT): number of correct responses in 90 s (Smith, 1982). Episodic long-term memory was tested with the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1983): number of words correctly recalled after presentation of a distractor list. Visuospatial function was tested with the Rey-Osterrieth Figure (Lezak, 1983): accuracy of copying a complex geometric design, scored on a 36-point scale.
The contribution of several clinical factors to performance on the dual-task paradigm was also evaluated. These included disease duration, disease severity as measured by the Extended Disability Status Scale (EDSS), depression with the Beck scale (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), fatigue with the self-rating Fatigue Severity Test (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), and the use of any centrally acting medications such as tricylic antidepressants or benzodiazepines.

Results

Baseline Task Performance

MS patients and controls were compared on the primary and secondary tasks when performed alone in order to determine if the level of difficulty of each task was discrepant between groups. There were no significant differences in baseline performance on the JLO task, \( t(49) = 0.21 \), humming, \( t(49) = 1.33 \), and alphabet reciting, \( t(49) = 0.20 \). MS patients as compared with controls were significantly slower when tapping with their right hands, \( t(49) = 2.7; p < .009 \), and left hands, \( t(49) = 2.4; p < .02 \). Mean baseline performance on each of these measures for MS patients and controls is shown in Table 1.

Dual-Task Performance

A Group (MS or controls) x Condition (single-task, dual-task) analysis of variance (ANOVA) was performed across all four secondary tasks (left-hand tapping, right-hand tapping, humming, and alphabet) with performance on JLO as the dependent measure. There was no significant main effect for group, \( F(1, 49) = 0.48 \). An effect for condition was found, \( F(1, 49) = 19.71 \); \( p < .0001 \), as well as a significant interaction effect, \( F(1, 49) = 8.37; p < .006 \). Planned \( t \) tests revealed that MS patients had a significantly greater decrement in performance compared with controls during the dual-task conditions, \( t(49) = 2.48; p < .01 \).

Next, Group x Condition ANOVAs during JLO and each of the secondary concurrent tasks were performed. No significant main effects for group were found; left finger tapping, \( F(1, 49) = 0.13 \); right finger tapping, \( F(1, 49) = 0.54 \); humming, \( F(1, 49) = 0.39 \); alphabet reciting, \( F(1, 49) = 0.004 \). There was no effect of condition found for left finger tapping, \( F(1, 49) = 2.51 \), or right finger tapping, \( F(1, 49) = 0.58 \). A significant effect of condition was found during humming, \( F(1, 49) = 27.47; p < .0001 \), and alphabet reciting, \( F(1, 49) = 26.50; p < .001 \), indicating that both MS patients and controls had a significant decrement in performance on the JLO task during concurrent performance of these secondary tasks. Moreover, there was a significant Group x Condition interaction during the humming condition, \( F(1, 49) = 4.76; p < .03 \), and alphabet reciting condition, \( F(1, 49) = 7.80; p < .008 \). This interaction was not significant during left finger tapping, \( F(1, 49) = 3.19 \), or right finger tapping, \( F(1, 49) = 0.85 \). Planned \( t \) tests revealed that MS patients had a significantly greater decrement in performance compared with controls during the humming, \( t(49) = 2.23; p < .03 \), and alphabet recitation dual-task conditions, \( t(49) = 2.73; p < .009 \), but did not differ from controls during the finger tapping dual-task conditions. Mean JLO performance alone (single-task condition) and when performed concurrently with each of the secondary tasks (dual-task condition) is shown in the Figure 1.

We also sought to rule out the possibility that there was a speed-accuracy tradeoff in controls that could account for better dual-task performance as compared with MS patients during the humming and alphabet reciting condition. We analyzed the number of JLO test items that were completed during each of these dual-task conditions. Controls completed more JLO test items than MS patients during both concurrent humming, \( t(49) = 2.76; p < .008 \), and alphabet reciting, \( t(49) = 2.41; p < .02 \). Thus, controls did not slow their JLO performance in order to increase accuracy during the dual-task conditions.

Performance on Neuropsychological Measures

As a group, we found that MS patients were impaired on several executive measures as compared with controls (see Table 2). We sought to determine if performance on these measures were associated with dual-task performance in MS patients. We used JLO performance during concurrent humming or alphabet recitation as indicators of dual-task performance because these conditions differed significantly between

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Table 1

Baseline Performance (M ± SD) of Multiple Sclerosis (MS) Patients and Controls on Experimental Measures

<table>
<thead>
<tr>
<th>Task</th>
<th>MS</th>
<th>SD</th>
<th>Controls</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line orientation judgment</td>
<td>87.7</td>
<td>8.4</td>
<td>88.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Left hand tapping</td>
<td>100.4</td>
<td>29.9</td>
<td>120.5</td>
<td>17.7</td>
</tr>
<tr>
<td>Right hand tapping</td>
<td>117.2</td>
<td>21.1</td>
<td>133.0</td>
<td>18.3</td>
</tr>
<tr>
<td>Humming a melody</td>
<td>77.9</td>
<td>24.7</td>
<td>69.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Reciting the alphabet</td>
<td>143.8</td>
<td>41.6</td>
<td>151.1</td>
<td>38.1</td>
</tr>
</tbody>
</table>
were performed with clinical measures, but no significant
relationship was found between being on a medication and
diminished motor performance in MS patients. This could have
resulted in poorer performance during the dual-task condition
by MS patients as well, but this was not observed. This
dissociation between cognitive and motor secondary tasks
emphasizes the validity and specificity of the dual-task proce-
dure for cognitive dysfunction.

An important factor to consider when analyzing perfor-
ance of dual-task paradigms in patients and controls is the
difficulty of the individual tasks. It has been noted that a
decrement in performance during a dual-task condition may
merely reflect an absolute increase in difficulty of the tasks for
patients compared with controls (Badddeley, Bressi, Della Sala,
Logie, & Spinnler, 1991). In our study, it was found that there
was no difference between group performance on JLO, hum-
ing, or alphabet recitation when performed alone. Thus,
impaired dual-task performance by MS patients on our para-
digm is not likely to be due to nonspecific differences in task
difficulty. On two of our secondary tasks, left and right finger
tapping. MS patients were worse than controls in baseline
performance, and this may have been due to relatively compro-
mised motor performance in MS patients. This could have
resulted in poorer performance during the dual-task condition
by MS patients as well, but this was not observed. This
dissociation between cognitive and motor secondary tasks
emphasizes the validity and specificity of the dual-task proce-
dure for cognitive dysfunction.

An alternative proposal forwarded to account for a decre-
ment in performance during dual-task paradigms has been that
there is anatomical interference between tasks. This hypoth-
esis claims that tasks sharing a common cerebral space will
cause greater interference with each other than tasks sub-
served by distinct brain regions (Kinsbourne & Hicks, 1978).
Our results indirectly address this claim. Because the JLO task
may be predominantly a right hemisphere task (Benton,
Hannay, & Varney, 1975), it is possible that humming, also
assumed to be subserved by the right hemisphere, would cause
greater interference than alphabet reciting, more likely to be
subserved in part by the left hemisphere. Our findings do not
support this claim in MS patients or controls because both
humming and alphabet recitation tasks caused a decrement in
JLO performance. However, we do not have any direct
evidence as to the exact degree of overlap between the brain
regions supporting each of these tasks.

It is our hypothesis that the decrement in performance

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<td><strong>Comparison of Multiple Sclerosis (MS) Patients and Controls on Neuropsychological Measures (M ± SD)</strong></td>
</tr>
<tr>
<td>Measure</td>
</tr>
<tr>
<td>Digit span forward</td>
</tr>
<tr>
<td>RAVLT</td>
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<tr>
<td>Symbol Digit Modalities</td>
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<tr>
<td>Semantic fluency</td>
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<tr>
<td>Executive</td>
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<tr>
<td>Categories</td>
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<tr>
<td>Perservations</td>
</tr>
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</table>

Note. RAVLT = Rey Auditory Verbal Learning Test; PASAT = Paced Auditory Serial Addition Test; WCST = Wisconsin Card Sorting Test.

*p ≤ .01.

MS patients from controls. A decrement score for MS patients and controls was calculated that reflected the difference in performance during the dual-task condition as compared with the single-task condition (i.e., baseline JLO performance minus JLO performance during humming divided by baseline JLO performance). The decrement scores for each of the dual-task conditions (i.e., humming and reciting) was correlated with performance on executive measures. A significant correlation was found only in MS patients during the alphabet condition of the dual-task and PASAT performance (r = .50, p < .007).

We also sought to investigate the possibility that performance on the dual-task paradigm may be due to a nonspecific general decline in cognitive performance in MS patients. MS patients were not impaired as compared with controls on measures of digit span, verbal episodic memory, or visuospatial function (see Table 2). Dual-task decrement scores were also correlated with performance on these neuropsychological measures. This analysis failed to reveal a significant correlation with digit span (humming: r = .15 and alpha: r = .21), delayed recall of a supraspan list (r = .20 and .22), or copying the Rey–Osterrieth figure (r = .22 and .10). Similar analyses were performed with clinical measures, but no significant correlations were found between the dual-task decrement scores and disease duration (r = .09 and .12), EDSS score (r = .05 and .04), the Beck depression scale (r = .22 and .20) or the fatigue measure (r = .19 and .06). Only 7 out of 36 MS patients were taking centrally active medications and no relationship was found between being on a medication and dual-task decrement scores using a median split to define good and bad performers (humming contingency coefficient = 0.02 and reciting: 0.10).

**Discussion**

MS patients and controls showed a decrement in performance on a primary task when a secondary task was performed concurrently. Within the working memory model of Baddeley (1986), secondary tasks may place increased demands on the CES that is responsible for allocating appropriate attentional resources in working memory during cognitive challenges such as these. In our dual-task paradigm, finger tapping resulted in a minimal decrement in performance on the primary task in both MS patients and controls. We hypothesize that this was because finger tapping requires minimal resource allocation by the CES. In contrast, humming a lullaby and reciting the alphabet resulted in a significantly greater decrement in MS patients than controls in performance on JLO during the dual-task condition. We hypothesize that these secondary tasks make greater demands on the CES than finger tapping. Thus, these results support our hypothesis that the CES of working memory is impaired in MS patients.

The first r values in parentheses refer to the correlation between each of the neuropsychological and clinical measures and humming decrement, and the second r values refer to the correlation between each of the neuropsychological and clinical measures and the alphabet decrement.
observed during the dual-task condition reflects the inability of the CES to allocate sufficient attentional resources to support accurate performance of these tasks concurrently. This notion is also consistent with Norman and Shallice’s (1980) model of attentional control of action. In this model, a supervisory attentional system (SAS), analogous to the CES, is called on during situations such as the performance of a novel task or when established automatic processes have to be overridden. Overloading the SAS thus should lead to degraded task performance. In our paradigm, concurrent performance of a JLO task with humming or alphabet reciting caused a greater overload in MS patients than controls, suggesting that MS patients have limited CES functioning. To more fully understand the specific processes that may be responsible for the breakdown of the CES in MS patients, it will be necessary to devise additional dual-task paradigms.

We also explored other cognitive factors that may be related to impairments in the CES of working memory. There was a significant correlation in MS patients between dual-task performance and the PASAT. Performance on this measure relies heavily on speed of information processing (Gronwall, 1977), as presumably does the coordinating function of the CES. Other studies of MS patients have also documented impaired information processing speed (Litvan, Grafman, Vendrell, & Martinez, 1988; Rao, Aubin, Le., 1989). This significant correlation suggests that impaired cognitive processing speed may contribute to poor performance under dual-task conditions. A recent study has also postulated that working memory impairments in MS may be due to impairments in the speed and capacity of central information processing (Grigsby et al., 1994). In this study, poor performance was found on digit span, the Brown–Peterson paradigm, and immediate logical memory in a group of chronic progressive MS patients during disease activity. Furthermore, performance on these measures correlated with a measure of semantic fluency. Although the CES of working memory was not tested directly, these findings provide converging evidence to support our observation of a relation between impaired working memory and information processing speed in MS patients. Other studies that have found dysfunction of phonological loop of working memory (Litvan, 1988; Rao et al., 1993). Because another measure used in our study that relies in part to speed of information processing, the symbol digit test did not significantly correlate with dual-task performance, further work will be required to confirm the contribution of information processing resources to adequate CES functioning.

Dual-task performance did not correlate with the other measures of executive function. This finding suggests that the CES and processes probed by clinical measures of executive function may be dissociable. Finally, factors such as general intellectual decline, poor neurological status, depression, fatigue, or medications were not found to influence dual-task performance, emphasizing the specificity of impaired dual-task performance for compromised cognitive functioning.

Several caveats must be kept in mind when interpreting our findings. First, whereas we studied a relatively large number of MS patients, this group of patients represented a large proportion of patients with relapsing–remitting MS as compared with chronic progressive disease. The former group has been shown to be less impaired cognitively (Grossman et al., 1994), and it is therefore possible that we have underestimated the extent of working memory impairments in the population of MS patients. Second, we did not relate patterns of performance on the dual-task paradigm to neuroanatomical factors that may contribute to impairments in MS patients such as the volume and anatomic distribution of demyelinating plaques seen on MRI. Other investigators have found a correlation between the Wisconsin Card Sorting Test (WCST) and frontal lobe plaque burden (Arnett et al., 1994). They hypothesized frontal lobe white matter lesions rather than total lesion burden accounts for the executive function deficits found in MS patients. We have recently demonstrated with functional neuroimaging that the prefrontal cortex is activated during dual-task performance (D’Esposito, in press) and also hypothesize that CES deficits in MS patients may be related to either frontal plaque burden or an interruption of pathways projecting to the frontal lobes by plaques in other locations. Because dual-task performance did not correlate with the WCST, the frontal regions that subserve the processes underlying the WCST and dual-task paradigms may be distinct. Regional analysis of plaque burden in MS patients with working memory impairments will be necessary to test this hypothesis. We conclude that the impairment on our dual-task paradigm in MS patients reflects a specific cognitive deficit within working memory reflecting an impaired central executive system.

References


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