Impairment in working memory in multiple sclerosis

Osama Abourelmaged El-Kholy[a], Mohamed Ramadan[a], Mahmoud El-Sheikh[b] and Moataz Ali[a]

Departments of [a]Neuropsychiatry and [b]Radiology, Alexandria University, Alexandria, Egypt

Correspondence to Osama Abourelmaged El-Kholy, Department of Neuropsychiatry, Alexandria University, 724 Elhoria St. Loran, Alexandria, Egypt
Tel: +20 122 271 4118; fax: + 035830280;
e-mail: oskholy@yahoo.com

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Aim

The aim of the current study was to assess the relation between working memory dysfunction and clinical and MRI findings in relapsing remitting multiple sclerosis.

Participants and methods

This study was conducted on 50 patients with clinically definite relapsing remitting multiple sclerosis, they were recruited from the Outpatient Clinic of Alexandria University Hospitals; and 25 healthy controls matched for age, sex, and educational level. All participants were subjected to neuropsychological assessment that included: digit span, visual span, *N*-nack task, and Wisconsin card sorting test. The patient group was further subjected to: Expanded disability status scale (EDSS) and brain MRI.

Results

Clinically, the present study found no statistically significant correlations between working memory dysfunction and age, age at onset, sex, number of relapses, affected functional system, or EDSS status. Alternatively, there were statistically significant positive correlations between working memory dysfunction and the duration of illness.

Conclusion

This study suggests that according to the resources utilized by cognitive tasks, working memory tasks may be classified into high-demanding working memory tasks (2-back task and WCST) and low-demanding working memory tasks (1-back task and digit and visual span), and in relapsing remitting multiple sclerosis working memory dysfunction includes mainly high-demanding working memory tasks.

Keywords:

MRI, multiple sclerosis, working memory

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Introduction

Cognitive impairment is a common clinical feature of multiple sclerosis (MS), occurring in up to 65% of patients with this disorder (Foong *et al.*, 1998). Repeatedly, it has been suggested that the cognitive impairment in MS patients is strongly associated with limitations in work and social activities (DeSousa *et al.*, 2002).

Neuropsychological studies have provided evidence indicating that deficits in working memory (WM) may be involved in MS (Amato *et al.*, 2001). However, the brain mechanisms underlying these deficits continue to be a subject of ongoing investigations, as their patterning and specificity still remain unclear. This is particularly evident in psychophysiological research. The existing evidence indicates that the multifocal demyelination of MS leads to a disruption of the multiple interconnected brain areas, which form the substrate of the WM (Amato *et al.*, 2001).

The term 'working memory' was introduced into the literature of cognitive psychology by Miller *et al.* (1960). Their definition is surprisingly modern; they did foresee the goal-directed and executive components of WM:

> When we have decided to execute some particular plan, it is probably put in some special state or place where it can be remembered while it is being executed. Particularly if it is a transient, temporary kind of plan that will be used today and never again, we need some special place to store it. …we should like to speak of the memory we use for the execution of our plans as a kind of quick access, working memory.

They did not stop with a cognitive definition of WM, but went on and proposed an anatomical localization of these functions in the brain:

> This most forward position of the primate frontal lobe appears to us to serve as 'working memory' where plans can be retained temporarily when they are being formed, or transformed, or executed.

WM has a content and capacity. WM content is the task-relevant representations (representations are symbolic codes for information) temporarily held on-line during the delay of WM tasks. The content in WM is not only maintained (which is more in line with the definition of short-term memory), but can be manipulated by different operations, with the prospective aim of facilitating goal-directed behavior (external as motor execution or internal such as decision making). The content in WM is retained transiently (for seconds) and is not stored in long-term memory. If not actively maintained,

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the content disappears. One way to actively maintain the information in WM is to rehearse it (repetitively direct attention to it). Rehearsal supports WM, and protects the information from fading and possibly also from interference from competing stimuli (Raye *et al.*, 2002; Cowan, 2005).

WM capacity is the number of items of information that can be held active in parallel in WM. The capacity of WM is limited and a popular view is that seven (± 2) items of information can be processed simultaneously in WM, although one item can constitute a chunk of information (a chunk is a cluster of logically connected items, maintained as one), and thus extending the perimeter of seven. WM load quantifies the relative processing resources required to perform a WM task (Cowan, 2005; Klingberg, 2008).

A complex cognitive process such as WM is likely to be mediated by a distributed network of distinct brain regions (Mesulam, 1990). However, evidence from neuropsychological, electrophysiological, and functional neuroimaging studies in both animals and humans supports a role of the frontal lobes as a critical node in the network supporting WM (Groenewegen *et al.*, 1990). The frontal lobes make up over one-third of the human cerebral cortex and can be divided into three major subdivisions: the prefrontal cortex, the premotor/motor cortex, and the paralimbic cortex (which includes the anterior cingulated gyrus) (Uylings and Van Eden, 1990; Goldman-Rakic and Friedman, 1991). The prefrontal cortex is therefore situated to receive inputs from regions involved in the encoding and storage of information (i.e. parietal and temporal cortices), while projecting to regions involved in response initiation (i.e. basal ganglia). Such an anatomical profile is required for a structure involved in using internal representations to guide action (Selemon and Goldman-Rakic, 1988).

WM uses a network of cortical and subcortical areas. As it is dependent on this network, it may be disrupted by many neuropsychiatric disorders, including Alzheimer's disease, frontotemporal dementia, vascular dementia, Parkinson's disease, MS, head injuries, tumors, strokes, attention deficit hyperactivity disorder, schizophrenia, and reading disorder. The mechanisms by which these disorders cause deficits in WM are variable, complex, and, in most instances, poorly understood. The following mechanisms have been suggested: structural damage to the cortical or the subcortical network, demyelination and disconnection (MS), reduced prefrontal size, and disregulated prefrontal activity as a result of a reduction in subcortical input into the frontal cortex (reduced prefrontal catecholamine input) (Grace, 1991; Braver and Cohen, 1999; Friedman *et al.*, 1999; Durstewitz *et al.*, 2000; Russell *et al.*, 2000).

Aim of the work

The aim of the present work is to determine the relation between WM dysfunction and clinical and MRI findings in relapsing remitting MS.

Materials

This study was carried out on (a) 50 patients with clinically definite MS (according to Posers criteria) (Poser *et al.*, 1983) and a relapsing remitting course (according to the definition of Lublins and Reingolds) (Lublin and Reingold, 1996). They were recruited from the Outpatient Clinic of Alexandria University Hospitals in the period from October 2008 to August 2009. And (b) 25 healthy controls matched for age, sex, and educational level.

All participants were either included or excluded according to their fulfillment of the criteria below:

Inclusion criteria

(1) Age between 20 and 40 years.
(2) Sex; both men and women were included in the study.
(3) Written consent from each participant after explaining the nature, steps, and aim of the study.
(4) The study was approved by the Ethical Committee of the Alexandria Faculty of Medicine.

Exclusion criteria

(1) A current or a past medical or psychiatric disorder other than MS that could affect cognitive domains.
(2) Neurological impairment that might interfere with evaluation.
(3) MS relapse or corticosteroid use within the past 6 weeks.

Subjects and methods

All participants (patients and healthy controls) were subjected to the following:

(1) Complete history taking.
(2) A clinical assessment was carried out including the following:
    (a) Thorough physical, neurological, and psychiatric examination.
(3) A neuropsychological assessment was carried out including the following:
    (a) *Digit span subtest from the Wechsler adult intelligence scale-revised (Wechsler, 1981)*: This test requires the examiner to verbally present digits at a rate of one per second. The forward test requires the participant to repeat the digits verbatim. The backward test requires the participant to repeat the digits in the reverse order. The number of digits increases by one until the participant consecutively fails two trials of the same digit span length. The score for each participant was the maximum number of digits repeated correctly.
    (b) *Visual span subtest from the Wechsler memory scale-revised (Wechsler, 1987)*: This assessed participants' ability to remember a sequence of boxes lighting up on a computer screen. The visual span was calculated as the longest sequence that the participant could recall accurately on at least one of the two trials. For each trial, eight randomly

arranged white squares were shown on the screen. Some of the squares lit up in color, one by one, in a variable sequence and participants were instructed to remember the sequence. At the end of the presentation, the participant was required to touch each of the boxes that had lit up in the same order as they were originally presented. The task began with the simplest level of a two-box sequence. After each successful trial, the number of boxes in the sequence was increased by one to a maximum of nine. If the participant's response was incorrect at any particular level, an alternate sequence of the same length was presented. This continued until the participant failed two consecutive trials at any one level, whereupon the test was terminated. The visual span was calculated as the longest sequence that the participant could recall accurately on at least one trial.

(c) *N-back task (Parmenter et al., 2006)*: In this, the participant had to indicate whether a visual stimulus presented on the screen (the 'target' stimulus) was similar to or different from a previously presented stimulus (the 'cue' stimulus). This procedure required the relevant information to be maintained and updated in WM. The task was computerized. Participants were seated in front of a personal computer screen. Each *N*-back task consisted of three blocks of 15 responses to cue/target stimuli (16 stimuli presented to examine N-1 back task and 17 stimuli presented to examine N-2 back task). The maximal score for each task was 45 (15 trials $\times$ 3 blocks). Each stimulus was presented on the screen for 3000 ms. The participant had 3 s in which to answer 'same' or 'different'. After a 1000 ms interstimulus interval, a new stimulus appeared on the screen. All patients were given a training block of trials for the two levels of *N*-back task.

(d) *Wisconsin card sorting test (WCST) (64 card version) (Heaton, 1981*; *Gold et al., 1997)*: The participant was given one deck of 64 cards. The cards are printed with one to four different symbols (triangle, star, cross, and circle) and in one of four different colors (red, green, yellow, blue). The participant's task was to place the cards, one by one, under one of four different stimulus cards according to an undisclosed principle. The stimulus cards also contain symbols that differ according to number, shape, and color. The examiner informed the participant after each sort whether his or her placement was 'right' or 'wrong'. The participant had to deduce the principle on the basis of the feedback provided by the examiner. After a run of 10 consecutive correct placements, the underlying principle changed without this being disclosed to the participant. The test was concluded once a participant completed three correct runs of 10 correct placements or had exhausted all of the cards. Gold *et al.* (1997) have stated that 'successful WCST performance requires the subject to remember his or her prior response and associated feedback and to use this information to select a new response, a form of working memory'. A number of different scores can be derived, including the number of perseverative errors (the number of errors where the participant has used the same rule for their choice as the previous choice) and categories achieved (the number of run of 10 correct responses).

The patient group was further subjected to the following:

(1) *Expanded disability status scale (EDSS) (Kutzke, 1983)*: A patient was evaluated on the EDSS according to the signs and symptoms observed during a standard neurological examination. These clinical observations were classified into functional systems. There are eight functional systems, each grading the signs and symptoms for different neurological functions. The eight functional systems are pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other.

(2) Brain MRI including a T_1 pulse sequence, a T_2 pulse sequence, and a FLAIR pulse sequence. The site and number of MS plaques were determined in different regions of the brain.

Results

Demographic characteristics of the patients and the control groups

The age of the participants ranged between 21–39 and 21–37 years, with a mean of 29.32 ± 5.60 and 28.38 ± 5.32 for the patient and the control groups, respectively. There was no statistically significant difference between the patient and the control groups in terms of age ($P = 0.49$).

The patient group included 13 men (26.0%) and 37 women (74.0%), whereas the control group included 10 men (40.0%) and 15 women (60.0%). There was no statistically significant difference between the patient and the control groups in terms of sex ($P = 0.21$).

In terms of the educational level, 21 patients (42.0%) had primary or preparatory education, 18 (36.0%) had secondary education, 10 had higher education (20.0%), and one (2.0%) had postgraduate education, whereas among the control participants, 11 individuals (44.0%) had primary or preparatory education, seven (28.0%) had secondary education, six (24.0%) had higher education, and one (4.0%) had postgraduate education. There was no statistically significant difference between the patient and the control group in terms of education ($P = 0.87$) (Table 1).

Clinical findings

Table 2 shows that age at onset of the disease ranged from a minimum of 16 years to a maximum of 35 years, with a mean of 25.4 and a SD of 5. The duration of illness ranged between 1.00 and 11.00 years, with a mean of 4.18 ± 2.57. The number of relapses ranged between 2.0 and 11.0,

Table 1 Characteristics of the patients and the control groups in terms of age, sex, and education

Demographic variables	Patients	Controls	*t*	*P*
Age				
Range	21–39	21–37	0.697	0.49
Mean	29.32	28.38		
SD	5.596	5.327		
Sex				
Male	13 (26.0%)	10 (40.0%)	1.54	0.21
Female	37 (74.0%)	15 (60.0%)		
Education				
Primary or preparatory	21 (42.0%)	11 (44.0%)	0.71	0.87
Secondary	18 (36.0%)	7 (28.0%)		
Higher education	10 (20.0%)	6 (24.0%)		
postgraduate	1 (2.0%)	1 (4.0%)		

P is significant if <0.05.

Table 2 Clinical findings

Clinical variables	Minimum	Maximum	Mean	SD
Age at onset (years)	16.00	35.00	25.42	4.97
Duration of illness (years)	1.00	11.00	4.18	2.58
Number of relapses	2.00	11.00	4.36	1.98
Expanded disability status scale	0.00	3.50	2.29	0.99

with a mean of 4.36 ± 1.97. The EDSS ranged between 0.0 and 3.50, with a mean of 2.29 ± 0.99.

Magnetic resonance image findings

Table 3 shows the number of the lesions among the patient group. Five patients (10.0%) had a normal-appearing brain, 13 patients (26.0%) had less than five lesions, 16 patients (32.0%) had 5–10 lesions, nine patients (18.0%) had more than 10 lesions, and seven patients (14.0%) had dirty-appearing white matter.

Table 4 shows the level of lesions in the patient group. It shows that five patients (10%) had a normal-appearing brain, 26 patients had supratentorial lesions (52%), seven patients (14%) had infratentorial lesions, and 12 patients (24%) had lesions at both levels.

Table 3 Number of lesions

Number of lesions	Number of patients (%)
Normal-appearing brain	5 (10.0%)
<5	13 (26.0%)
5–10	16 (32.0%)
>10	9 (18.0%)
Dirty-appearing white matter	7 (14.0%)

Table 4 Level of lesions

Level of lesions	Number of patients (%)
Normal-appearing brain	5 (10%)
Supratentorial	26 (52%)
Infratentorial	7 (14%)
Both	12 (24%)

Table 5 Digit span: comparison of the results of the patients and the control participants

Digit span	Patients	Controls	*t*	*P*
Forward digit span				
Range	4–8	4–8	1.08	0.28
Mean	5.90	6.24		
SD	1.29	1.26		
Backward digit span				
Range	3–6	3–6	0.81	0.42
Mean	4.38	4.56		
SD	0.901	0.917		

P is significant if <0.05.

Results of neuropsychological assessments

Digit span

Table 5 shows the digit span – comparison of the results of the patients and the control participants. Forward digit span ranged between 4 and 8, with a mean of 5.90 ± 1.29 for the patient group, whereas for the control participants, it ranged between 4 and 8, with a mean of 6.24 ± 1.26. Backward digit span ranged between 3 and 6, with a mean of 4.38 ± 0.90 and 4.56 ± 0.91, for the patient and the control group, respectively. There were no statistically significant differences between the two groups studied in terms of forward digit span and backward digit span ($P = 0.28$ and 0.42, respectively).

Visual span

Table 6 shows the visual span – comparison of the results of the patient and the control group. Forward visual span ranged between 4 and 8, with a mean of 5.52 ± 1.35 and 6.12 ± 1.33 for the patient and the control group, respectively. Backward visual span ranged between 3 and 7, with a mean of 4.44 ± 1.12 and 4.92 ± 1.11 for the patient and the control group, respectively. There were no statistically significant differences between the patient and the control group in terms of visual span ($P = 0.072$ and 0.083, respectively).

N-back task

Table 7 shows the *N*-back task – comparison of the results of the patient and the control group. Performance of the studied groups in the 1-back task ranged between 35 and 45, with a mean of 40.20 ± 3.14 for the patient group, whereas for the control participants, it ranged between 37 and 45, with a mean of 41.60 ± 2.27; there was no statistically significant difference between them in the 1-back task ($P = 0.052$). Performance of the studied groups in the 2-back task ranged between 29 and 44, with a mean of 35.60 ± 4.10 for the patient group, whereas for the control participants, it ranged between 33 and 44, with a mean of 37.88 ± 4.02; there was a statistically significant difference between them in the 2-backtask ($P = 0.025$).

Wisconsin card sorting test

The results of the studied groups in the WCST are presented in Table 8. Categories achieved ranged between 0 and 3, with a mean of 1.84 ± 0.86 and 2.36 ± 0.90 for the patient and the control group, respectively. Perseverative errors ranged between 5 and 18, with a mean of 9.98 ± 2.535 for the patient group, and 6–16, with a mean of 8.36 ± 2.325 for the control participants. There were statistically significant differences

Table 6 Visual span: comparison of the results of the patients and the control participants

Visual span	Patients	Controls	*t*	*P*
Forward visual span				
Range	4–8	4–8	1.82	0.072
Mean	5.52	6.12		
SD	1.35	1.33		
Backward visual span				
Range	3–7	3–7	1.75	0.083
Mean	4.44	4.92		
SD	1.12	1.11		

P is significant if <0.05.

Table 7 *N*-back task: comparison of the results of the patient and the control group

N-back task	Patients	Controls	*t*	*P*
1-back task				
Range	35–45	37–45	1.98	0.052
Mean	40.20	41.60		
SD	3.14	2.27		
2-back task				
Range	29–44	33–44	2.03	0.025*
Mean	35.60	37.88		
SD	4.10	4.02		

*Significant difference between patients and control.
P is significant if <0.05.

Table 8 Wisconsin card sorting test (categories achieved and perseverative errors): comparison of the results of the patient and the control group

Wisconsin card sorting test	Patients	Controls	*t*	*P*
Categories achieved				
Range	0–3	0–3	2.4	0.018*
Mean	1.84	2.36		
SD	0.866	0.907		
Perseverative errors				
Range	5–18	6–16	2.67	0.009*
Mean	9.98	8.36		
SD	2.535	2.325		

*Significant difference between patients and control.
P is significant if <0.05.

between the patient and the control group in the categories achieved and perseverative errors ($P = 0.018$ and 0.009, respectively).

Correlations between working memory dysfunction and clinical findings

Table 9 and Figs 1–3 show statistically significant positive correlations between the duration of illness and the patients' performance on the WCST (perseverative errors and categories achieved) and the 2-back task, respectively ($P = 0.041$, 0.012, and 0.036).

Correlations between working memory dysfunction and radiological findings

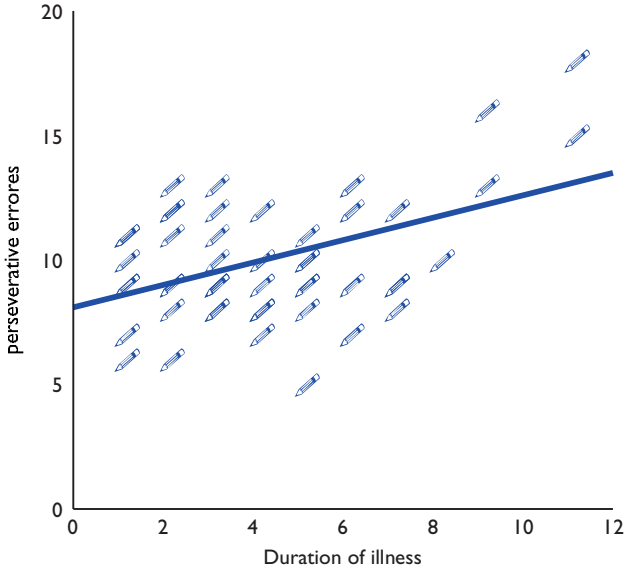
Table 10 and Figs 4–6 show that there were statistically significant positive correlations between the number of lesions and the patients' performance on the WCST (perseverative errors and categories achieved) and the 2-back task, respectively ($P = 0.041$, 0.004, and 0.048, respectively).

Table 9 Correlations between the duration of illness and the patients' performance on the 2-back task and the Wisconsin card sorting test (categories achieved and perseverative errors)

Duration of illness	*r*	*P*
WCST (perseverative errors)	0.457	0.041
WCST (categories achieved)	−0.453	0.012
2-Back task	−0.352	0.036

P is significant if <0.05.
WCST, Wisconsin card sorting test.

Figure 1



Correlation between the duration of illness and patients' performance on the Wisconsin card sorting test (perseverative errors).

Discussion

The current study proposed different psychometric tools to examine the different subcomponents of WM:

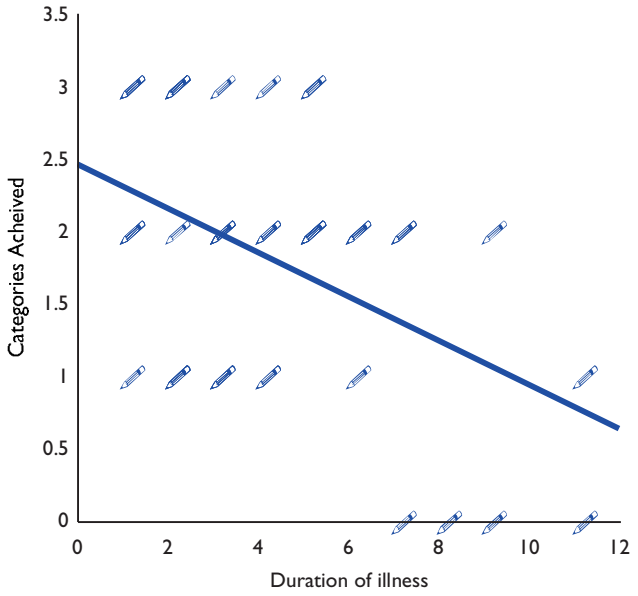
(1) Forward digit and visual span to evaluate controlling attention.
(2) Backward digit and visual span to measure controlling attention and the retentive subcomponent.
(3) *N*-back task to assess controlling attention, retentive, and updating subcomponents.
(4) WCST for task of controlling attention, retentive, updating and executive subcomponents.

There is no general agreement in the definition of reliable cut-off points for impairments in WM; thus, the present study defines dysfunction in WM as statistically significant differences between the patient and the control participants.

We found no statistically significant differences between the patients and the control participants in the performance on both the forward and the backward digit span test, in agreement with other authors (Rao *et al.*, 1991; Andrade *et al.*, 1999; Balsimelli *et al.*, 2007).

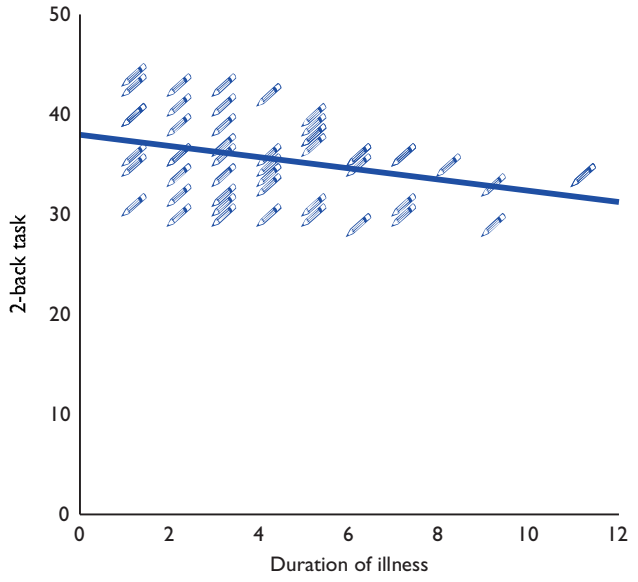
This results are not in agreement with those reported by Grigsby *et al.* (1994) and Sfagos *et al.* (2003), who found

Figure 2



Correlation between the duration of illness and the patients' performance on the Wisconsin card sorting test (categories achieved).

Figure 3



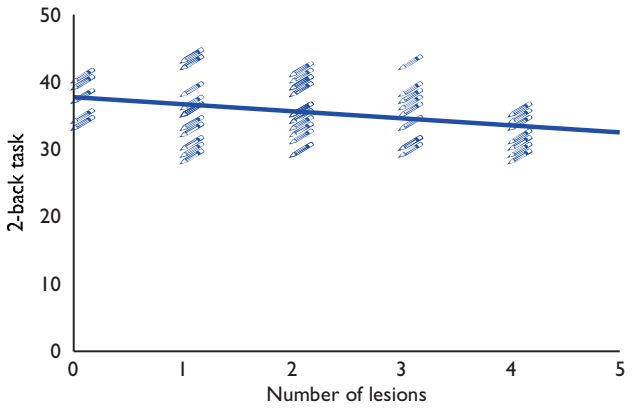
Correlation between the duration of illness and the patients' performance on the 2-back task.

Table 10 Correlations between the number of lesions and the patients' performance on the 2-back task and the Wisconsin card sorting test (categories achieved and perseverative errors)

Number of lesions	*r*	*P*
WCST (perseverative errors)	0.290	0.041
WCST (categories achieved)	−0.396	0.004
2-Back task	−0.281	0.048

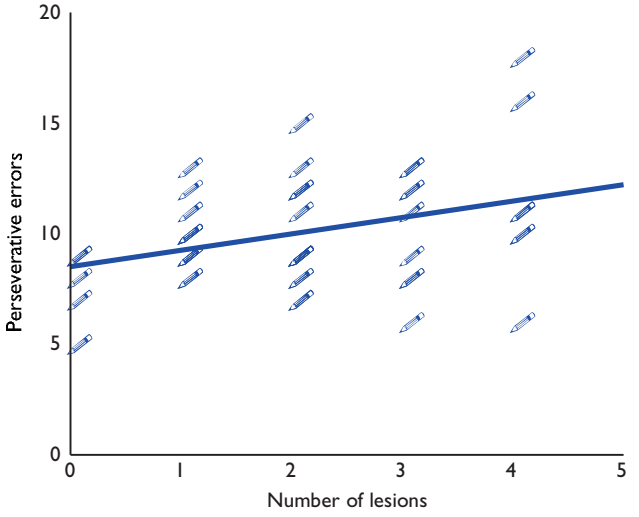
P is significant if <0.05.
WCST, Wisconsin card sorting test.

Figure 4



Correlation between the number of lesions and the patients' performance on the 2-back task.

Figure 5

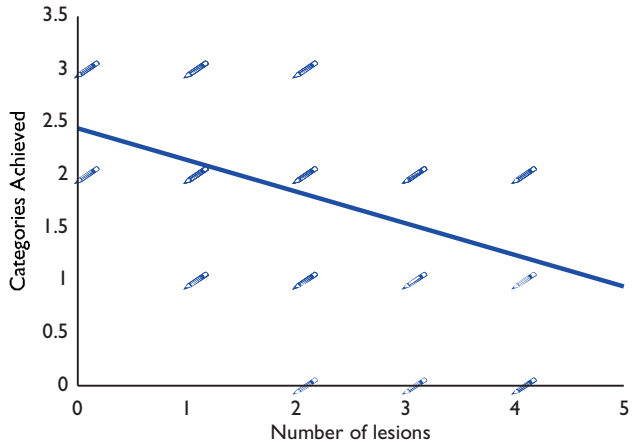


Correlation between the number of lesions and the patients' performance on the Wisconsin card sorting test (WCST) (perseverative errors).

statistically significant differences between the patients and the control participants in the performance on both the forward and the backward digit span test. The differences in these studies may be attributed to the fact that Grigsby and Sfagos carried out their studies on patients with a progressive course and recent relapse.

The current study showed no statistically significant differences between the patients and the control participants on visual span (forward and backward). This in agreement with Foong *et al.* (1998), who found statistically significant differences between the patients and the control participants in the performance on the visual span during relapse, but these differences did not exist during remission. However, in disagreement with our study, Foong *et al.* (1999) found statistically significant differences between the patients and the control participants in performance on the visual span. This

Figure 6



Correlation between the number of lesions and the patients' performance on the Wisconsin card sorting test (WCST) (categories achieved).

contradiction may be attributed to the differences in the selection criteria of the patients. In the current study, the maximum age of the patients was less than 40 years, patients on corticosteroid were excluded, the minimum time from the last relapse was 45 days, and the study was restricted to patients with a relapsing remitting course. Although in Foongs' study the maximum age of the patients was less than 50 years, other courses were involved and the minimum time from the last relapse was 30 days.

In the present study, there was no statistically significant difference between the patients and the control participants in performance on the 1-back task, but there was a statistically significant difference between the patient and the control group in performance on the 2-back task.

In the current study, there were statistically significant differences between the patient group and the control participants in performance on the WCST; the MS patients achieved fewer categories and made more perseverative errors than the control participants, confirming the results of several previous studies (Heaton *et al.*, 1985; Beatty *et al.*, 1990a; Mendozzi *et al.*, 1993; Beatty and Monson, 1996).

These results suggest that according to the resources utilized by cognitive tasks, WM tasks may be classified into high-demanding WM tasks (2-back task and WCST) and low-demanding WM tasks (1-back task and digit and visual span), and in relapsing remitting MS, dysfunction in WM includes mainly high-demanding WM tasks. That nature of dysfunction in WM in MS, which includes high-demanding working tasks, is different from the nature of dysfunction in WM in mania and schizophrenia, which includes low-demanding and high-demanding WM tasks (Conklin *et al.*, 2000; Perry *et al.*, 2001; Glahn *et al.*, 2006).

Clinically, this study found no significant correlations between dysfunction in WM and age, age at onset, sex, number of relapses, the functional system affected, or EDSS status. Alternatively, we found statistically significant positive correlations between dysfunction in WM and the duration of illness, which can be attributed to the degenerative nature of the illness (Frischer *et al.*, 2009).

The influence of disease characteristics on the cognitive processes in MS is a subject of controversy. Studies have shown an ambiguous relationship between duration of disease and cognition. Graf *et al.* (1984), McIntosh-Michaelis *et al.* (1991). Rao *et al.* (1987) reported no correlation between duration of disease and cognition. In contrast, a trend toward a higher frequency of poor scores in a memory test in patients with a longer disease duration was reported by Maurelli *et al.* (1992). Conflicting results have also been reported on the role of physical disability (measured using the Extended Disability Status Scale in most cases). Maurelli *et al.* (1992), Rao *et al.* (1987), and Stenager *et al.* (1989) reported significant correlations between physical disability and cognitive functioning. However, Beatty *et al.* (1990b) found that there were no significant correlations between physical disability and cognitive functioning.

Maurelli *et al.* (1992) and Rao *et al.* (1987) reported that the degree of cognitive impairment evident in individuals with MS seems to be unrelated to their neurological disability status or duration of disease. This is considered to be because of the variability in lesion sites. A patient with a predominantly spinal cord or optic nerve involvement may be severely physically disabled, but may have little or no cerebral demyelination and may therefore show little cognitive change. Feinstein *et al.* (1992) found that although duration of disease and disability were unrelated to cognitive impairment in their sample, the disease course seemed to be a sensitive marker of cognitive decline. They reported that a chronic-progressive disease course was associated with greater impairment in cognitive as well as sensory and motor domains.

However, the more commonly reported finding of an absence of any correlation between physical and cognitive functioning in patients with MS indicates that the latter cannot be ascertained from a neurological examination. Hence, a neuropsychological assessment may be valuable.

Radiologically, the present study found statistically positive correlations between the number of lesions and dysfunction in WM. An increase in the number of lesions led to more injury to intracortical and/or intercortical fibers. Injuries to this interconnecting white matter cause disconnection in WM and important processing regions. This study suggests disconnection as a potential mechanism for dysfunction in WM in MS. This is in agreement with Dineen *et al.* (2009), who suggested disconnection as a mechanism for cognitive dysfunction in MS.

Franklin *et al.* (1988) and Fulton *et al.* (1999) found that lesion volume was correlated with cognitive dysfunction in MS. They reported that the degree and pattern of cognitive dysfunction were correlated significantly with the amount of white-matter disease in the cerebral

hemispheres, as evidenced by MRI. This suggests that cerebral lesions result in cognitive dysfunction.

The present study found no correlation between dysfunction in WM and specific sites of lesions, and this may be attributed to the following: dependence of WM on diffuse, extensive neuronal circuits that include cortical and subcortical structures and the inability of conventional MRI to detect lesions in normal-appearing white matter. Therefore, the lesions are more diffuse and involve more sites than those that appear as MRI hyperintensities.

To enhance specificity, a considerable number of studies have focused on identifying the relationship between the location of MS lesions and cognitive dysfunction. These studies fall into two general classes of examination: effects of 'disconnection' and effects of regionally circumscribed lesion load. As focal lesions are quite common and often extensive in the cerebral white matter, disconnection syndromes would be expected to be common. However, numerous correlations have been reported between the location of MS lesions and cognitive impairment (Sperling *et al.*, 2001; Rovaris *et al.*, 2006). Many of these studies have yielded conflicting results, which can partially be attributed to the heterogeneous pathological substrate of multiples sclerosis lesions. Beyond methodological concerns, particularly for MS, the significance of the results is limited because of the lack of the pathological specificity of contrast-enhanced MRI, the heterogeneous pathological substrate, and its inability to detect magnetic resonance-related diffuse changes in normal-appearing brain tissue. The application of quantitative magnetic resonance techniques, such as magnetization transfer imaging, diffusion tensor imaging, and magnetic resonance spectroscopy, has been shown to at least partially overcome the lack of pathological specificity of conventional MRI. The evidence that normal-appearing white matter is not normal remains central for understanding the mechanisms of dysfunction in WM in MS.

Conclusion and recommendation

(1) According to the resources utilized by cognitive tasks, WM tasks may be classified into high-demanding WM tasks and low-demanding WM tasks.
(2) WM dysfunction in relapsing remitting MS includes high-demanding working tasks.
(3) There were no statistically significant correlations between dysfunction in WM and age, sex, age at onset, number of the relapses, intensity of clinical disability, or the functional system affected.
(4) There were statistically significant positive correlations between dysfunction in WM and the duration of illness.
(5) There were no statistically significant correlations between dysfunction in WM and site of the lesions.
(6) There were statistically significant positive correlations between dysfunction in WM and the number of lesions.

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Conflicts of interest

There are no conflicts of interest.

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