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Short-Term Memory Impairment Sparing the Central Executive in Relapsing-Remitting Multiple Sclerosis?

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Abstract

Objective: It is widely accepted that working memory (WM) impairment has a high incidence in multiple sclerosis (MS). However, this WM impairment has rarely been analyzed with reference to a cognitive model. The aim of the study was to determine whether dysfunction in MS is due to WM or short-term memory deficits.

Methods: We assessed the components of Baddeley's WM cognitive model, which include the phonological loop, visual sketch and central executive. Seventeen conditions implicating short term memory and executive functions (flexibility, inhibition, manipulation) were carried out by128MS patients diagnosed with RRMS, and 30 age matched healthy controls. Also assessed were three tasks of motor speed namely the Overt articulation rate, Digit-symbol copy test and Digit-symbol coding test.

Results: In all but three conditions, the MS group scored significantly below the control group (Mann-Whitney tests), suggesting a short-term memory deficit in MS. However, when performances in the central executive conditions were expressed proportionally to a baseline, the patient group behaved in a similar way to the control group. Finally, no relationship could be shown between the impairment in WM tasks and the motor speed tasks.

Conclusions: Our results suggest an impairment of short-term memory in MS patients but with a relative preservation of WM. Critically, this conclusion is not in agreement with the widespread notion of WM deficit in MS

Keywords: Multiple sclerosis; Working memory; Short-term memory; Central executive; Relapsing-remitting; Phonological loop; Visual sketchpad; Speed

Introduction

The current study addressed the issue of working memory (WM) impairment in relapsing-remitting multiple sclerosis (RRMS) patients, employing the definition of WM based on Alan Baddeley's model [1-3] in cognitive psychology. Built on previous existing models of short-term memory, this structural model [2-4] proposed the existence of two subsystems that are dependent upon a third attentionally-limited control component, the central executive. According to Baddeley, the phonological loop subsystem deals with verbal and acoustic information while the visuospatial sketchpad processes visual and spatial material. More recently, a fourth subsystem, the episodic buffer, has been added and is suggested to relate WM with long-term memory [1] by integrating information from multiple sources. The phonological loop has, itself, been divided into two subcomponents: the phonological store and the articulatory rehearsal system. The former is a temporary storage system that holds memory traces over a matter of seconds while the latter is responsible for refreshing these memory traces that would otherwise disappear at the end of the few-seconds delay. This articulatory rehearsal system is held to involve a subvocal rehearsal component, which not only maintains the information within the store, but also permits the transfer of visual information to the phonological store, provided the items can be named [3]. The phonological loop, which is by far the best-developed component of the WM model, has been suggested to be particularly suited to the retention of sequential auditory information. The phonological loop also appears to play an important role in long-term phonological learning, being associated with the development of vocabulary in children and the speed of acquisition of foreign language vocabulary in adults [5]. The visuospatial sketchpad is held to maintain visual and spatial information that is either directly perceived or internally generated by mental imagery. Logie [6] proposed to fractionate this component into a visual storage subcomponent (visual cache) and a more dynamic retrieval component (inner scribe), leading to the concepts of a visual store that mainly deals with color and shape, and a dynamic store, that is concerned with motor and kinesthesic information. The visual store is held to show a close connection with attention and action whereas the dynamic store is believed to share resources with spatial attention and oculomotor control [7]. The sketchpad serves the function of integrating spatial, visual and possibly kinesthetic information into a unified representation that may be temporarily stored and manipulated. The central executive is generally considered the main factor determining individual differences in WM span [3,8]. It tends to be highly correlated with tasks of complex cognitive skills, such as standard measures of intelligence [9]. For these reasons, damage to the central executive is likely to lead to the most disabling impairment of WM. The central executive component can be fractionated into a number of executive subprocesses [10,11]. An important point to note is that the two slave systems (phonological loop and visual sketchpad) relate simply to short-term storage, while it is the central executive that is taken to support WM, by means of supplementary processes carried out on this stored information.

An important limitation in the MS literature is that tests previously used to assess WM in these patient populations have also been sensitive to other factors and have thus precluded the specific assessment of WM components [12]. This is illustrated in two of the most frequently used tests in the MS literature, the PASAT and the digit span. The Paced Auditory Serial Addition Test (PASAT) consists of a series of randomized digits presented at a regular rate with the task of the subject being to add each new heard digit to the digit immediately preceding it. Abnormal performances on the PASAT were initially emphasized by Rao in his seminal paper on MS cognition [16] before being widely documented by the John DeLuca team [13-17]. Clinically isolated syndromes (CIS) and RRMS tend to present relatively preserved abilities compared to progressive forms of MS [18-22]. fMRI investigations, however, suggest that even in cases of normal performance, a more extensive and bilateral network may be recruited in early MS patients compared to healthy participants [18,22,23]. This phenomenon is generally viewed as a compensatory mechanism [20-24]. Thus, it would appear that the clinical form as well as the stage of MS could be relevant factors for the PASAT, although RRMS forms are relatively spared. According to Baddeley's model, the update needed for the PASAT involves the central executive, which refreshes the memory content to adapt to changing stimuli. Depending on digit format (heard or seen), the phonological loop or the visual sketchpad is also required. Because of the many causes of perturbation in this task, it is not possible to attribute a deficit to a specific working memory component. In addition, other cognitive factors, such as slowing and/or arithmetic impairment may confound the interpretation of WM deficits [25].

After the PASAT, the second most commonly used test of short-term abilities in MS patients is the digit span, requiring the immediate serial recall of a list of spoken digits. In an initial part, the subject is required to repeat digits in the same order as presented (forward span) and in a second part, to repeat them in the reverse order (backward span). The two conditions rely on the phonological loop, while the backward span also relies on the central executive. Thus, a proposition of the involvement of a central executive impairment can only be put forward in the presence of a pathological decline of the backward span in comparison to the forward span. The Corsi Block-tapping task [26] was originally developed as a non-verbal analogue of the digit span and can be regarded as a measure of spatial WM. The examiner taps blocks in a given sequence and as in the digit span task, participants are required to repeat the sequence immediately after the examiner has finished (forward and backward conditions are tested). In MS, digit spans have tended to be more widely used than block spans and impaired global digit spans have been reported in CIS as well as in various clinical forms of MS [22] including RRMS [24]. Normal performances have also been found [27,28]. For all these papers however, no dysexecutive conclusion could be drawn since forward and backward spans were taken together in a global score. Morgen reported that the length of the backward span is correlated with cortical atrophy (as measured by VBM) and not white matter damage [21,29] but, in these studies, once again, the forward span was overlooked. Studies that have considered the two digit scores separately have only on one occasion [30] shown an impairment restricted to the backward span that would be suggestive of a deficit of the central executive. Most studies have reported either a deficit (in RRMS and secondary progressive MS [31]; in CIS [32]; in non specified clinical forms [17]) or a preservation of both digit spans (in RRMS and secondary progressive MS [33]; in RRMS [34,35]; in various clinical forms [36]). The same controversy applies to block spans with studies reporting either a backward span selectively affected [33], or both spans impaired (in various clinical forms [36]) or preserved (in RRMS [34]; in CIS [32]).Thus, RRMS patients may show a deficit in span tasks, for both digits and blocks. However, in this MS form, few studies have reported the combination of a pathological backward span and a preserved forward span [30,33] that would, in Baddeley's view, be suggestive of a dysfunctional central executive. Another methodological consideration concerns the variability in the strategies applied to digit stimuli, even in healthy subjects. The verbal task can be approached with visuospatial strategies (spontaneous visualization strategies) making it possible that visuospatial computations contribute to performance of the auditory digit span task. This in turn precludes as analysis according to a single component in Baddeley's model.

The objective of the present study was to test the hypothesis of WM deficits in RRMS patients using tasks that allow inferences relative to the multi-component model of Baddeley. In addition to carrying out assessment of the phonological loop and the sketchpad, we also considered functions of flexibility, inhibition and manipulation of the central executive. In the event that deficits were indeed observed in patients we planned to examine the possibility of a relationship between performance in these tasks and several speed cues (motor speed and articulation rate).

Method

Participants

The study included prospectively patients consulting to three French MS centres. To be included, patients needed to meet the diagnosis of RRMS according to the McDonald criteria [37] and with an EDSS ≤6. The exclusion criteria were the presence of (1) cognitive impairments related to a neurological illness other than MS (prior head injury, stroke, brain tumor, etc), (2) a known psychiatric disorder, ongoing depression or a neurotic disease, (3) a history of drug, alcohol dependence or learning disability, (4) an exacerbation of symptoms over 3 months at the time of testing, (5) a corticosteroid infusion within 4 weeks prior to evaluation, and (6) an auditory or visual impairment that could interfere with cognitive assessment. Finally, 128 RRMS patients were included (94 females; 34 males) with mean age 39.6±9.6 years (range: 18-64 years) and mean disease duration 10.6± 6.6 years (range: 1-27 years). The scores using the Expanded Disability Status Scale (EDSS) ranged from 0 to 6 (mean: 2.1±1.5, median: 2). Performances were compared to 30 age-matched healthy controls (19 females; 11 males), who served as a control group (mean age: 37 years±12.6, range: 19-62 years). The protocol was approved by the research ethics board of Reims hospital and all participants gave their informed consent.

Cognitive assessment

The WM tasks used in the current study were issued from a larger neuropsychological battery conducted in a multi-centre project. The subcomponents of the phonological loop were assessed by means of both the word-length effect (short-long words) and articulation speed (mono, tri and pentasyllabic words) for the articulatory rehearsal, and the phonological similarity effect (similar/dissimilar letters) for the phonological store. The visual and dynamic subcomponents of the sketchpad were tested with a matrix test and a block-tapping task respectively. The central executive was investigated mainly in terms of manipulation (alpha span) and, to a lesser extent, inhibition and flexibility (Stroop in four conditions adapted from Bohnen and colleagues [37]). Two less-specific tasks of WM were also applied: PASAT [39] and digit spans [40]. Each of the aforementioned tasks are described below followed by a description of their theoretical links with the multi-component model.

Tasks assessing global WM

PASAT: Recorded stimuli were presented every 3 seconds using a CD [39]. A ten-digit practice series was conducted before the 60 test pairs. The total and the percentage of correct responses were considered. According to Baddeley, the verbal and auditory format of the digits would implicate both the phonological loop and the update process, the central executive.

Digit span: The Digit Span subtest (French version of the WAIS-R) was administered [40]. The standard scores, calculated according to Wechsler's classical procedure, correspond to the total number of sequences successfully completed for both forward and backward orders taken together. According to Baddeley's tripartite model, both forward and backward span tasks rely on the phonological loop [41] but only the latter involves the central executive (digits manipulation). As standard scores do not dissociate forward and backward responses, the longest series successfully completed in forward and reverse order were also separately considered here. The longest series successfully completed succeeded on the two trials were discarded if they were of the same length in order to remove attentional variations non-specific to WM.

Tasks specifically designed to assess working memory subcomponents according to Baddeley's model

WM components		Behavioural variables
Central executive	Manipulation	Digit forward vs backward spans
		Corsi forward vs backward spans
		Alphabetical vs serial recalls from the alpha span task
	Inhibition	Interference vs naming times= interference score from the Stroop test
	Flexibility	Flexibility vs interference times= flexibility score from the Stroop test
Phonological loop	Articulatory rehearsal component	Long vs short words spans= word-length effect
	Phonological store	Similar vs dissimilar letters spans = phonological similarity effect
Visual sketchpad	Visual component	Matrices spans
	Dynamic component	Forward Corsi block-tapping spans
Table 1 summarizes the links between the behavioural variables considered here and the different WM components of Baddeley's model.		

Table 1. Behavioural variables in relation to Baddeley's model components.

Phonological loop tasks

Articulatory rehearsal component. In healthy subjects, evidence for the rehearsal component is provided by the word-length effect, spans being better for short words than for longer ones (i.e. pub, dog, arm versus auditorium, university, organization) as polysyllablic words take more time to rehearse. This component was assessed by tasks taken from the Côte des Neiges [42], a WM battery in the French language. Two sets of words were used: monosyllabic and tetrasyllabic words. Words of each set were matched according to the frequency of occurrence. Testing was stopped when none or only one sequence of the three trials of the same length was successfully completed. The final score corresponds to the total number of correctly reported sequences. To avoid attentional bias and rather focus on WM mechanisms, we considered the longest series successfully completed for monosyllabic and tetrasyllabic words respectively. We thus stopped when all sequences of the same length were failed. In Baddeley's view, a reduction in span for long words compared to short ones reflects a preservation of the articulatory rehearsal component. If this word-length effect is observed in healthy participants, its size should also serve to establish a reference for RRMS patients.

Phonological store. In healthy subjects, the integrity of this component is classically expressed by sensitivity to phonemic interference: the phonological similarity effect. Spans are better (longer series of items accurately remembered) when words or letters are dissimilar compared to when they are similar in sound (i.e. pit, day, cow, pen versus man, cat, map; K, R, X, B versus C, V, B, D). To remove the influence of long-term lexical representations, the phonological similarity effect was assessed here using letters rather than words. Tasks were once again selected from the Côte des Neiges battery [42]. Two sets of seven letters were used for constructing the sequences of similar (rhyming letters in French: B, C, D, G, P, T, V) and dissimilar items (non-rhyming letters in French: F, H, L, J, K, R, M).As with the articulatory rehearsal component, we strayed from the original administration by measuring the longest sequences correctly recalled (and not the number of correct trials) for similar and dissimilar letters respectively. A reduction in span for similar letters compared to dissimilar ones was taken to reflect a preservation of the phonological store.

Visuospatial sketchpad tasks

Visual component: This static component of the visual sketchpad is usually tested by the matrix task [43]. Following the presentation of a matrix containing some filled squares, the subject is required to indicate on an empty matrix which cells were previously filled.

Dynamic component: The dynamic component was measured with the Corsi block-tapping task (MEM-III, [44]). This test consists of nine blocks mounted on a black board arranged in a random pattern, numbered on the examiner's side. The examiner taps the blocks in a given sequence at a rate of approximately one per second. In a first part, participants are required to repeat the block sequence immediately after the examiner has finished, and in a second part in the reverse order. So as to focus on WM processes, the highest number of blocks correctly completed in forward and backward orders were considered and not the total score (number of successfully completed sequences) as recommended in Wechsler manual.

Central executive tasks

The phonological loop and the visual sketchpad support the simple storage of short-term information. The central executive is assessed with tasks that involve an active processing of this stored information. However, since an impairment of one of the two slave systems will also lead to a deficit in central executive tasks, executive conditions are classically interpreted according to baseline conditions, with the functioning of the central executive inferred from the difference between these conditions.

Alpha span task. The alpha span task [45] compares the recall of words in the same order as heard (storage only) with recall in alphabetical order (storage and manipulation).The length of the lists is also adapted according to the individual word span of the participant. As the storage requirement was equated between the two conditions, the only expected difference was the intervention of the central executive during the alphabetical condition [46]. In controls, lower performance was thus predicted in the alpha span task as compared to the serial recall task. In RRMS patients, we assumed that an impairment of the central executive would be expressed by a greater decrease, relative to controls, for the alphabetic as compared to the serial recall.

Stroop test. The Stroop test requires subjects to read the name or to name the colors of patches or words. We applied a version of the Stroop test adapted from Bohnen [37]. Besides the three classical trials (color naming, N: name the colors of colored patches; word reading, R: read color names printed in black; color-word interference: name the color of words printed in a different color), a fourth flexibility trial (F) was added. In this trial, stimuli and task were identical to the color-word interference trial except that some words were framed, and subjects were required to read these words instead of naming the color. A hundred items (patches or names of four colors: green, blue, red and yellow) arranged in orderly rows and columns were presented in a trial. In agreement with recommendations from Lezak [46], the total time needed to name or read the stimuli was recorded. To better dissociate the effect of slowing (characteristic of MS patients) from the temporal increase due to other cognitive processes, three further scores were calculated. To take into account difficulties in lexical access, a naming score was established from the reading time (N time-R time/R time*100). To examine executive processes, we calculated an interference score (I time-N time/N time*100) from the reading time and a flexibility score (F time- I time/I time*100) from the interference time. Errors (self-corrected and not) were also considered. For the flexibility trial, two types of errors were obtained: color errors, whereby the subject read instead of named the color and word errors, whereby the subject kept naming instead of reading for the framed stimuli.

Tasks of motor speed

Three tasks of motor speed were used.

Overt articulation rate: Neuropsychological data suggesting dependence between the subvocal rehearsal and the overt articulation rate [47]. This overt articulation rate was nevertheless introduced here to obtain a measure of the articulation speed, according to the usual slowing observed in MS. Three lists of 10 words each, graduated in word length (1, 3 and 5 syllables), were presented five times successively. Subjects had to read each list, continuously and as fast as possible, five times. The total duration (in seconds) needed to articulate the 10 words 5 times was recorded.

Digit-symbol copy test: The number of symbols correctly copied (digit symbol-copy optional subtest from the WAIS-III? [48]) provided an index of copying speed. This test is argued to be particularly sensitive to motor slowing [49, 50].

Digit-symbol coding test: As often used in the MS literature, the classical standard score of the digit-symbol coding test (WAIS-R, [40]) was also scored.

Statistical evaluation

The normality of distributions and the homogeneity of variances were assessed with the Kolmogorov-Smirnof and the Cochran tests respectively. As most of our data did not meet these criteria, simple comparisons were tested with non-parametric tests (Mann-Whitney and Wilcoxon). However, as several of our hypotheses depended on the comparison of MS patients and healthy participants on more than one variable (i.e. forward and backward spans), parametric ANOVAs with repeated-measures were applied to look for interaction effects. When significant effects were shown in this latter case (main effects or interactions), follow up post-hoc comparisons were conducted with non-parametric tests. Correlations were assessed using the Spearman correlation test. Statistical analyses were performed using StatView for Windows (SAS Institute Inc., USA, Version 5.0). Statistical significance was set at $p<.05$.

Results

Demographical data

Control and RRMS groups were comparable for age (Mann-Whitney: $U= 1639.5$, $p=.21$) and education ($U=1639.5$, $p=.21$). Only marginal effects of sex were observed on WM or speed performances for the control group (span for dissimilar words: U=52, p<.03, females span being shorter than males ones; articulation rate for the first reading of the second list: U=47; p<.02, females being slower than males) and the RRMS group (articulation rate for the first reading of the first and second lists: U=680.5, p<.02; U=697.5, p<.02, females being faster than males in both conditions).

WM performance

WM performances of RRMS patients and control participants are described in Table 2. All participants had valid data for most WM measures used in the current study. In some cases, there were some missing values due to vagaries of clinical testing (mainly timing pressures). However, except for the PASAT (13 patients declined the task), no participant wished to discontinue participation or was excluded for cognitive reasons.

Working memory tasks	MS patients	Controls	Mann-Whitney
Non-specific tasks			
	n=115	n=30	
PASAT score	40.12 (11.9)	49.5 (10.04)	U=895.5, p<.0001
PASAT %	66.76 (19.79)	82.48 (16.73)	U=884, p<.0001
	n=127	n=30	
Digit span (standard scores, WAIS-R)	9.47 (2.83)	11.4 (3.17)	
Digit forward span	5.94 (1.13)	6.43 (1.1)	U=1484.5, p>.05
Digit backward span	4.42 (1.28)	5.23 (1.33)	U=1657.5, p>.05
Articulatory rehearsal component			
	n=126	n=30	
Short-word span (1 syllable words)	4.56 (0.84)	5.23 (0.97)	U=1184.5, p=.0008
Long-word span (4 syllables words)	3.8 (0.68)	4.27 (0.78)	U=1263, p=.002
	n=100	n=28	
Phonological store component			
	n=126	n=30	
Dissimilar-letter span	4.59 (0.9)	5.4 (0.93)	U=1026, p<.0001
Similar-letter span	4.64 (1.03)	5.16 (1.08)	U=1377.5, p=.02
Dynamic component			
	n=126	n=30	
Corsi forward span	5.52 (0.97)	6.23 (1.04)	U=1193.5, p=.0009
Corsi backward span	4.98 (0.94)	5.6 (0.77)	U=1198.5, p=.001
Visual component			
	n=125	n=30	
Pattern span	7.52 (1.56)	8.2 (1.63)	U=1449, p>.05
Central executive component			
α span test	n=126	n=30	
Initial word span	4.49 (0.72)	4.93 (0.83)	U=1307.5, p=.004
Serial recall	9.06 (1.42)	9.47 (0.68)	U=1737, p>.05
Alphabetical recall	7.08 (2.75)	8.1 (2.04)	U=1428.5, p>.05

Manipulation score	-23.2 (27.72)	-14.52 (20.64)	U=1461, p>.05
Stroop test	n=116	n=30	
Reading: raw time	47.46 (9.87)	41.97 (7.42)	U=1181, p=.002
Naming: raw time	69.62 (15.02)	61.33 (10.98)	U=1172.5, p=.002
Interference: raw time	124.49 (50.91)	100.1 (20.27)	U=1134.5, p=.002
Flexibility: raw time	140.76 (49.67)	113.97 (23.82)	U=1071, p=.001
Naming score	16.98 (19.15)	14.26 (10.83)	U=1777.5, p>.05
Interference score	75.27 (58.01)	63.85 (23.23)	U=1748, p>.05
Flexibility score	4.49 (0.72)	4.93 (0.83)	U=1682, p>.05
Reading: corrected-errors	0.22 (0.61)	0.1 (0.4)	U=1699.5, p>.05
Naming: corrected-errors	0.69 (1.06)	0.57 (0.82)	U=1778, p>.05
Interference: corrected-errors	1.67 (2.15)	1.2 (1.45)	U=1609.5, p>.05
Flexibility: corrected-color-errors	1.82 (2.21)	1.3 (1.39)	U=1596, p>.05
Flexibility: corrected-word-errors	1.37 (3.13)	0.37 (0.61)	U=1537.5, p>.05
Reading: non-corrected-errors	0.11 (0.36)	0.03 (0.18)	U=1740.5, p>.05
Naming: non-corrected-errors	0.23 (0.77)	0.1 (0.31)	U=1780.5, p>.05
Interference: non-corrected-errors	0.73 (1.39)	0.3 (0.6)	U=1558, p>.05
Flexibility: non-corrected-color-errors	0.34 (0.75)	0.1 (0.31)	U=1365.5, p>.05
Flexibility: non-corrected-word-errors	0.17 (0.58)	0.07 (0.25)	U=1671, p>.05

Table 2. Working memory performances of both groups.

Tasks assessing global WM

PASAT: Non-parametric Mann-Whitney tests revealed that RRMS patients obtained lower scores than controls for both total and percentage of correct responses (correct responses: U= 895, p<.0001; percentages: U=884, p<.0001).

Digit span: The digit span scores of RRMS patients and healthy participants were transformed into standard scores according to the instructions in the published manual (WAIS-III, [48]). The comparison between groups was carried out with Mann-Whitney tests. RRMS patients obtained lower standard scores than healthy participants (U=813.5, p=.0001).

With regard to the longest series successfully completed, the influence of repetition order (direct/reverse) was examined using a repeated-measures ANOVA with Group (healthy participants, RRMS patients) as the between-subject factor, and Order (forward, backward) as the within-subject factor. We found a significant main effect of Order, backward spans being shorter than forward ones (F(1,155)=105.82, p<.001), and a significant main effect of Group, spans of RRMS patients being shorter than those of healthy participants (F(1,155)=9.94, p=.002). There was no significant Group x Order interaction (F(1,155)=1.53, p>.05).

Tasks specifically designed to assess working memory subcomponents according to Baddeley's model

Phonological loop tasks

Articulatory rehearsal component assessment: A statistical analysis of the word-length effect was carried out using a repeated-measures ANOVA, with Group (healthy participants, RRMS patients) as the between-subjects factor, and Length (short, long words) as the within-subjects factor. We found a significant main effect of Length (F(1,154)=, p<.0001), short-words yielding longer spans than long-words, and Group (F(1,154)=17.02, p<.0001), spans of RRMS patients being worse than those of healthy participants. The Group x Length interaction was not significant (F(1,154)=1.72, p>.05), suggesting a similar word-length effect in the two groups.

Phonological store assessment: The phonological similarity effect was analysed with a repeated-measures ANOVA with Group (healthy participants, RRMS patients) as the between-subjects factor, and Phonology (dissimilar, similar) as the within-subjects factor. Only the main effect of Group was significant (F(1,154)=14.96, p=.0002), RRMS patients obtaining poorer performances than controls. The ANOVA failed to show any significant main effect of Phonology (F(1,154)=.84, p>.05) or Group x Phonology interaction (F(1,154)=2.22, p>.05). Non-parametric tests (Wilcoxon) confirmed that, for both groups, the difference between similar and dissimilar items was not significant.

Visuospatial sketchpad tasks

Visual component: Corsi span performance for forward and backward conditions was assessed by an ANOVA with Group as a between-subject factor (healthy participants, RRMS patients), and Order (direct, reverse) as a within-subject factor. A significant main effect of Group was demonstrated (F(1,154)=17.02, p<.0001), spans of RRMS patients being shorter than those of healthy participants. A significant main effect of Order was also observed (F(1,154)=31.70, p<. 0001) but the Group x Order interaction was not significant (F(1,154)=.17, p>.05).

Dynamic component: For the matrix task, no statistical difference was revealed between RRMS patients and healthy participants for the memory of visual patterns (U=1449, p>.05).

Central executive tasks

Alpha span task the results of the alpha span task revealed a significant difference between the groups for the baseline condition (U=1307, p<.009), word span of RRMS patients being worse than those of healthy participants. However, when individual performance was considered in the subsequent recalls, no significant difference was observed either for the serial recall (U=1737, p>.05) or for the alphabetical one (U=1428.5, p>.05). A repeated-measures ANOVA with Group (healthy participants, RRMS patients) as the between-subject factor, and Recall (serial, alphabetical) as the within-subject factor was performed. A main effect of Recall was demonstrated (F(1,148)=59.36, p<.0001): as predicted, alphabetical recall was worse than serial recall. Only a tendency was observed for the main effect of Group (F(1,148)=3.75, p=.05), MS patients tending towards lower performance than healthy controls. The interaction Group x Recall didn't reach significance (F (1,148)=2.19, p>.05).

Stroop test For the Stroop test, the time taken to carry out the task increased from trial to trial for each group (Wilcoxon values not reported here). RRMS patients were significantly slower than healthy participants in every trial (Mann-Whitney tests on raw times), suggesting abnormal lexical access, interference sensitivity and cognitive flexibility. However, when slowing was not considered from raw times but expressed proportionally between the times, the differences between groups were no longer significant (Mann-Whitney tests on scores). None of the differences between groups revealed significances for the errors, corrected or not.

Tasks of motor speed

Overt articulation rate Table 3 presents the results of controls and RRMS for the three tasks of motor speed.

Processing speed tasks	MS patients	Controls	Mann-Whitney
Overt articulation rate			
Time (seconds) to articulate (1 syll. words)	3.75 (1.04)	2.98 (0.57)	U=813.5, p<.0001
Time (seconds) to articulate (3 syll. words)	5.34 (1.36)	4.47 (1.12)	U=872.5, p=.0005
Time (seconds) to articulate (5 syll. words)	8.71 (2.23)	7.21 (2.06)	U=773, p<.0001
Digit-symbol copy test			
	n=126	n=30	
Nb of symbols correctly copied	98.56 (29.04)	122.27 (14.53)	U=974.5, p<.0001
Digit-symbol coding test			
	n=127	n=30	
Standard score	8.82 (3.29)	12.3 (2.91)	U=833.5, p<.0001

Table 3. Processing speed performances of both groups.

An analysis of variance was performed on the articulation speed (time in seconds to articulate a list of words). We first considered the mean time of the five measures obtained for each of the three lists. There was a main effect of Group (F(1,260)=12.86, p=.0005), RRMS patients being slower than controls to repeat the words, and a main effect of List (F(2,256)=647.22, p<.0001), showing a classical word-length effect: whereby time to repeat the lists were longer for pentasyllabic words as compared to trisyllabic words and for trisyllabic words as compared to monosyllabic ones (all these differences being significant using Wilcoxon tests). There was also a Group x List interaction, the difference between the groups increasing with word-length.

Digit-symbol copy and digit-symbol coding tests: For the digit-symbol tests, RRMS patients copied significantly less symbols (U=974.5, p<.0001) and obtained lower standard scores (U=833.5, p<. 0001) than controls.

Correlations between performances of RRMS and motor speed Correlations between the three indices of motor speed and impaired performances of RRMS patients were examined (Table 4). The articulation rate was considered in terms of the first articulation time for each list: one, three and five syllables words. We expected to find higher correlations between digit-symbol copy scores and tasks implying manual responses (i.e. Corsi block-tapping task) as compared to oral responses (i.e. digit span). Conversely, a higher correlation was predicted to exist between articulation rates and tasks implying oral responses as compared to manual responses.

	First time (seconds) to articulate (1 syll. words)	First time (seconds) to articulate (3 syll. words)	First time (seconds) to articulate (5 syll. words)	Digit-symbol copy test (WAIS-III)	Digit-symbol coding test (WAIS-R)
PASAT score	-.019, NS	-.086, NS	-.115, NS	.211, p=.0245	.558,* p<.0001
PASAT %	-.023, NS	-.089, NS	-.121, NS	.213, p=.0231	.566,* p<.0001
Digit forward span	-.055, NS	-.018, NS	-.051, NS	-.143, NS	.278, p=.0018
Digit backward span	-.135, NS	-.204, p=.0437	-.248, p=.014	.262, p=.0034	.342, p=.0001
Short-word span (1 syll. words)	.014, NS	-.029, NS	-.007, NS	.117, NS	.246, p=.006
Long-word span (4 syll. words)	-1,948E-4, NS	.041, NS	.065, NS	.112, NS	.212, p=.0176
Articulatory speed Time (seconds) to articulate (1 syll. words)	.828,* p<.0001	.764,* p<.0001	.726,* p<.0001	-.605,* p<.0001	-.343, p=.0007
Time (seconds) to articulate (3 syll. words)	.737,* p<.0001	.931,* p<.0001	.842,* p<.0001	-.586,* p<.0001	-.266, p=.0084
Time (seconds) to articulate (5 syll. words)	.637,* p<.0001	.817,* p<.0001	.930,* p<.0001	-.639,* p<.0001	-.228, p=.0239
Dissimilar-letter span	-.131, NS	-.075, NS	-.158, NS	.211, p=.0183	.363, p<.0001
Similar-letter span	-.127, NS	-.187, NS	-.177, NS	.289, p=.0012	.301 p=.0008
Corsi forward span	-.07, NS	-.175, NS	-.086, NS	.257, p=.004	.243, p=.0067
Corsi backward span	.005, NS	-.017, NS	-.01, NS	.086, NS	.225, p=.0118
α span test Initial word span	-.109, NS	-.122, NS	-.078, NS	.239, p=.0076	.243, p=.0066
Stroop test Reading: raw time	.375, p=.0003	.396, p=.0001	.382, p=.0002	-.287, p=.0015	-.524,* p<.0001
Naming: raw time	.295, p=.0041	.383, p=.0002	.409, p<.0001	-.34, p=.0002	-.545,* P<.0001
Interference: raw time	.329, p=.0015	.416, p<.0001	.409, p<.0001	-.303, p=.001	-.534,* p<.0001
Flexibility: raw time	.285, p=.0071	.314, p=.0031	.306, p=.0039	-.355, p=.0001	-.614,* p<.0001

Table 4. Correlations between the three indexes of processing speed and impaired performances of RRMS patients

The two indices of motor slowing were negatively correlated (digit-symbol copy and articulatory rates). Aside from correlations between articulatory speeds, no relevant correlation was obtained between articulatory rates and the WM performances of RRMS patients. For the digit-symbol copy test, the only observed correlations were between the articulatory rates, a longer time to articulate being linked to fewer copied symbols. For the standard score of the digit-symbol coding, positive correlations were found with the PASAT (the number of correct responses in the digit-symbol coding was linked to the number of correct responses with the PASAT for both raw score and percentage), and negative correlations with the four conditions of the Stroop test (the number of correct responses in the digit-symbol coding correlated negatively to the time to complete the Stroop conditions).

Discussion

In the present study, we examined the functioning of WM components in RRMS patients and healthy controls in terms of the Baddeley model [1-7]. Seventeen conditions implicating short term memory and executive functions (flexibility, inhibition, manipulation) were carried out and we observed that in all but three conditions (the matrix task and the serial and alphabetical recalls from the alpha span), the patient group scores were significantly below the control group. However, while considered globally, our RRMS patients showed a deficit in short-term memory abilities, consistent with the prevailing view of WM impairment as a cognitive feature of MS, cognitive analysis of the same performances suggested a normal WM processing, for the central executive in particular.

The two tasks assessing global WM (digit spans and PASAT) revealed impairments in RRMS patients who obtained shorter spans compared to controls for forward and backward measures. To our knowledge, few studies on RRMS have separately considered the two digit scores for both digit spans. Restricted impairment of the backward span was not found in the current study, as exceptionally reported in a previous paper [30]. Nor was there a significant decline in backward as compared to the forward span in RRMS patients, which would indicate a deficit of the central executive. We observed that the PASAT revealed abnormal performance in our patients. While functional neuroimaging literature have suggested an abnormal network early in the disease [18,22-24], no clear deficit has been shown in RRMS in particular [18-20,22]. One reason for the current results could be the more severe damage in our RRMS patients, who obtained an EDSS higher than that reported in other studies for similar disease duration.

We carried out an analysis of the short-term deficit according to Baddeley's WM model. With regard to the phonological loop, the same classical word-length effect (short versus long words) was observed in both groups, suggesting the integrity of the articulatory rehearsal component in RRMS patients. For the phonological store (phonologically similar versus dissimilar letters), RRMS patients performed worse than controls for both similar and dissimilar items. However, their results could not be attributed to an impairment of the phonological component since we did not observe the classical phonological similarity effect even in healthy participants. Importantly, the failure to observe the classical phonological similarity effect may be due to a linguistic bias in Quebec and France, as some meaningless sequences of letters in the Canadian battery [42] unfortunately correspond to French acronyms. With regard to the visuospatial sketchpad, the performances of RRMS patients in the matrix task did not differ from those of control subjects, in support of a functioning visual component in RRMS group. For the dynamic component, assessed with the Corsi block-tapping task, shorter spans were observed in RRMS patients as compared to controls for both forward and backward spans. The same applies to Corsi block spans with studies reporting either a selective backward span [33], or impairments (in various clinical forms [36]) or preservation (in RRMS [34]; in CIS [32]) in both spans. Our results indicated dynamic component impairment in RRMS. However, the deleterious effect of manipulation as compared to simple storage (backward versus forward spans) appeared to be proportional for both groups. This result suggests a relative preservation of the central executive in RRMS. The same pattern of performance was observed for the digit spans. Despite a deficit in RRMS patients for both repetition orders, a similar decrease between forward and backward spans was observed in the two groups. Convergent results were found in the tasks designed to assess subcomponents of the central executive. For the alpha span task, the difference between serial and alphabetical recalls, which is often taken to reflect the involvement of the central executive, appeared to be similar in both groups. Similarly, for the Stroop test, the relative timing performances of RRMS patients through the four conditions corresponded to those of healthy participants provided that their slowing had been controlled. While the raw times of the RRMS groups were longer than those of the control group in interference and flexibility conditions, this difference disappeared when time is expressed according to the other conditions. Whereas a clear slowing was demonstrated in RRMS patients for this test, no evidence for an impairment of their central executive was shown. In sum, our RRMS patients showed a deficit in short-term memory but cognitive analysis of the same performances suggests a normal WM processing, for the central executive in particular. Critically, this conclusion is not in agreement with the widespread notion of WM deficit in MS [12,28,30,51-68]. Our findings here would need to be confirmed with other studies but nevertheless they emphasize the necessity of accurately choosing the fitting methodology (tasks and behavioural factors) for draw definitive conclusions.

WM deficits in RRMS patients could be, in part, the consequence of more basic factors such as slowing. However, despite the use of two indices quantifying manual and vocal speeds respectively, no correlation could be shown between the impairment in WM tasks and the motor speed. Several studies have reported a contribution of processing speed to WM [53,54,59,69,70]. One possibility is that the present difficulties of RRMS patients are explainable by a bradyphreny, in the absence of motor slowing. It is of interest that the only correlations observed here were between the two most demanding tasks (PASAT, Stroop) and the digit-symbol coding. This test is taken to be relatively unaffected by intellectual level, memory or learning [71,72]. Contrary to our two indices of pure motor slowing (digit symbol-copy and articulatory rates), the digit-symbol coding may nevertheless assess some associated cognitive processing speed. Our results demonstrate the difficulty in assessing slowing in neuropsychological studies, as frequently reported in MS literature [70].

A final important result of the present work concerns the central executive. RRMS patients exhibit normal performance for all the subprocesses considered here: manipulation (backward digit span, backward bloc span, alpha span), flexibility and inhibition (Stroop). This preservation does not appear to be due to a bias in RRMS sample (which could be cognitively well-preserved) since this good executive functioning was observable despite short-term impairment. This result has pertinence for everyday life, as central executive is both believed to be an important determinant of individual differences in WM span, and to be involved in high level processes [3,8,9]. For cognitive rehabilitation, these results also demonstrate the importance of using a detailed component analysis to avoid unnecessary WM or executive training. Finally, with regard to longitudinal studies, the results shown here may explain why only a slow executive decrease is usually reported in follow-up despite apparent early dysfunction [28].

In summary, we developed in this study a methodology which allowed us to assess the different components of Baddeley's WM model in MS patients. Our results support the hypothesis of an isolated impairment of both slaves systems (phonological loop and visual sketchpad), causing a simple disruption of short-term storage. On the contrary, we found no argument suggesting a disruption of the central executive, a third component which allows additional processes to be carried out on short-term stored information (flexibility, manipulation, inhibition,...). In this preliminary study, the relative small sample of patient may weaken our results, in relation to patients selection bias. Although we carefully analyzed these potential biases (such as disease duration, EDSS stage, educational level, type of MS medicine…) without finding any significant effect, our results have to be corroborated on a larger sample.

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